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HIV
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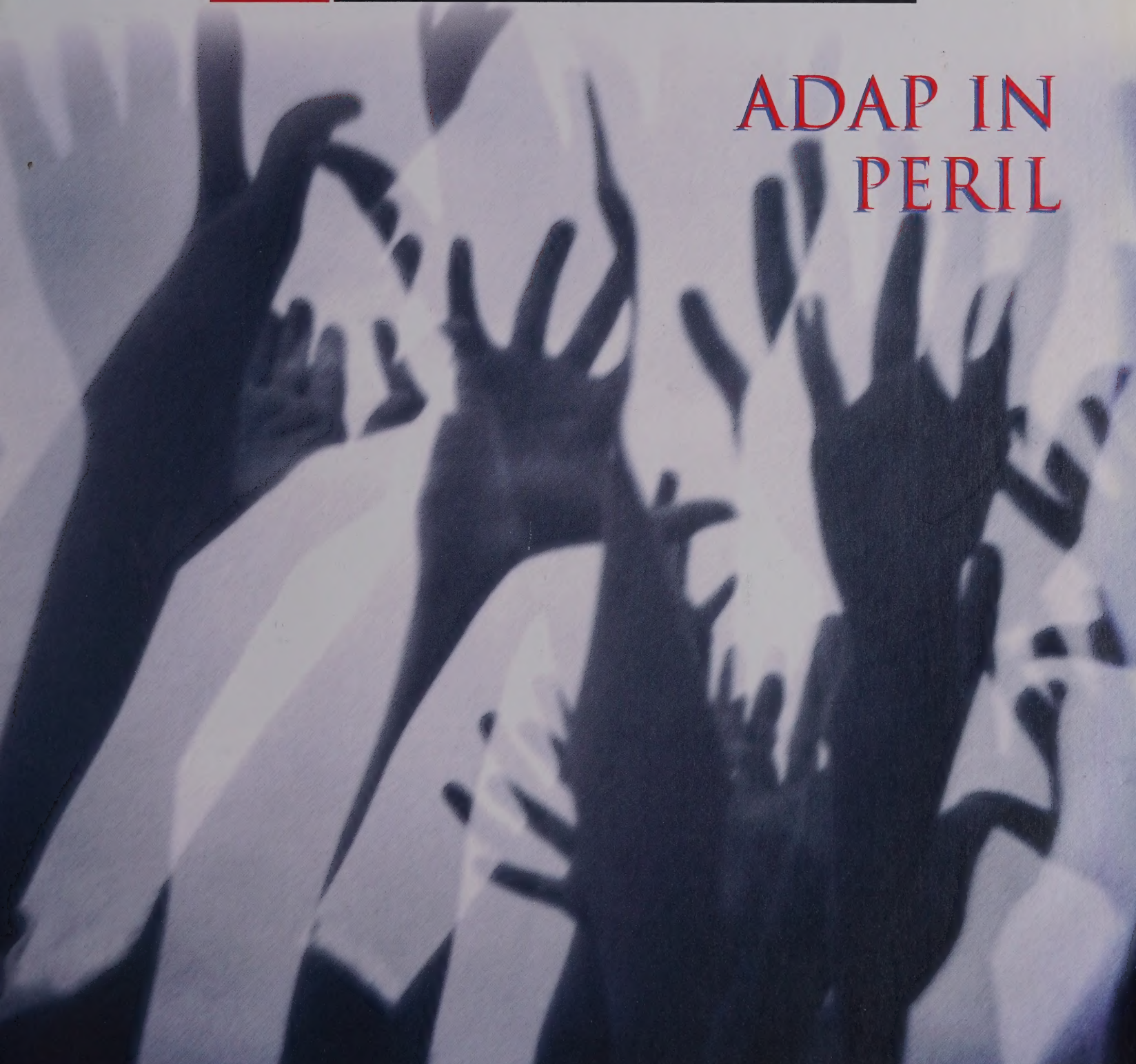
ADAP IN PERIL



CBO/AGENCY COPY COMPLIMENTS OF ROCHE PHARMACEUTICALS

Details on use of TRIZIVIR

- TRIZIVIR treats HIV infection alone or in combination with other HIV medicines. There is little information about its use in patients with large amounts (>100,000 copies) of virus in their blood. At this time, it's not known whether taking TRIZIVIR will slow the progress of HIV disease or help you live longer.
- TRIZIVIR does not cure HIV infection/AIDS or prevent passing HIV to others.

Important Safety Information

TRIZIVIR contains abacavir sulfate, which is also called ZIAGEN®. About 1 in 20 patients (5%) who take abacavir (as TRIZIVIR or ZIAGEN) will have a **serious allergic reaction** (hypersensitivity reaction) that **may cause death if the drug is not stopped right away.**

You may be having this reaction if:

(1) you get a skin rash, or

(2) you get 1 or more symptoms from at least 2 of the following groups:

- Fever
- Nausea, vomiting, diarrhea, abdominal (stomach area) pain
- Extreme tiredness, achiness, generally ill feeling
- Sore throat, shortness of breath, cough

If you think you may be having a reaction, **STOP taking TRIZIVIR and call your doctor right away.**

If you stop treatment with TRIZIVIR because of this serious reaction, **NEVER take abacavir (as TRIZIVIR or ZIAGEN) again.** If you take any of these medicines again after you have had this serious reaction, **you could die within hours.**

NO FOOD OR WATER RESTRICTIONS

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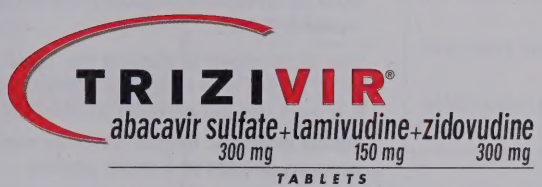

The only 3-in-1 pill regimen

Ask your doctor if TRIZIVIR is right for you.

Some patients who have stopped taking abacavir (as TRIZIVIR or ZIAGEN) and who have then started taking abacavir again have had serious or life-threatening allergic (hypersensitivity) reactions. If you must stop treatment with TRIZIVIR for reasons other than symptoms of hypersensitivity, do not begin taking it again without talking to your healthcare provider. If your healthcare provider decides that you may begin taking abacavir (as TRIZIVIR or ZIAGEN) again, you should do so only in a setting with other people to get access to a doctor, if needed.

A written list of these symptoms is on the Warning Card your pharmacist gives you. Carry this Warning Card with you.

Make sure to see your doctor regularly because serious side effects can occur, such as muscle damage and a decrease in red and/or white blood cells, especially in patients with advanced HIV disease or AIDS.

A buildup of lactic acid and severe liver problems, including fatal cases, have been reported with HIV drugs of this type, including the medicines in TRIZIVIR and other antiretrovirals.

Changes in body fat may occur in some patients taking antiretroviral therapy. The cause and long-term health effects of these conditions are not known at this time.

The most common side effects of taking the medicines in TRIZIVIR together are nausea, vomiting, diarrhea, loss of appetite, weakness or tiredness, headache, dizziness, pain or tingling of the hands or feet, and muscle and joint pain.

Please see important information for TRIZIVIR on adjacent page.

www.TRIZIVIR.com

gsk GlaxoSmithKline

MEDICATION GUIDE

TRIZIVIR® (TRY-zih-veer) Tablets

Generic name: abacavir sulfate, lamivudine, and zidovudine

Read the Medication Guide you get each time you fill your prescription for Trizivir. There may be new information since you filled your last prescription.

What is the most important information I should know about Trizivir?

Trizivir contains abacavir, which is also called Ziagen®. About 1 in 20 patients (5%) who take abacavir (as Trizivir or Ziagen) will have a **serious allergic reaction** (hypersensitivity reaction) that **may cause death if the drug is not stopped right away**.

You may be having this reaction if:

(1) you get a skin rash, or

(2) you get 1 or more symptoms from at least 2 of the following groups:

- **Fever**
- **Nausea, vomiting, diarrhea, abdominal (stomach area) pain**
- **Extreme tiredness, achiness, generally ill feeling**
- **Sore throat, shortness of breath, cough**

If you think you may be having a reaction, **STOP taking Trizivir and call your doctor right away.**

If you stop treatment with Trizivir because of this serious reaction, **NEVER take abacavir (as Trizivir or Ziagen) again.** If you take any of these medicines again after you have had this serious reaction, **you could die within hours.**

Some patients who have stopped taking abacavir (as Trizivir or Ziagen) and who have then started taking abacavir again have had serious or life-threatening allergic (hypersensitivity) reactions. If you must stop treatment with Trizivir for reasons other than symptoms of hypersensitivity, do not begin taking it again without talking to your health care provider. If your health care provider decides that you may begin taking abacavir (as Trizivir or Ziagen) again, you should do so only in a setting with other people to get access to a doctor if needed.

A written list of these symptoms is on the Warning Card your pharmacist gives you. Carry this Warning Card with you.

Trizivir can have other serious side effects. Be sure to read the section below entitled "What are the possible side effects of Trizivir?"

What is Trizivir?

Trizivir is a medicine used to treat HIV infection. Trizivir includes 3 medicines: Ziagen (abacavir), Epivir® (lamivudine or 3TC®), and Retrovir® (zidovudine, AZT, or ZDV).

All 3 of these medicines are called nucleoside analogue reverse transcriptase inhibitors (NRTIs). When used together, they help lower the amount of HIV in your blood. This helps to keep your immune system as healthy as possible so it can fight infection.

Different combinations of medicines are used to treat HIV infection. You and your doctor should discuss which combination of medicines is best for you.

Trizivir does not cure HIV infection or AIDS. Trizivir has not been studied long enough to know if it will help you live longer or have fewer of the medical problems that are associated with HIV infection or AIDS. Therefore, you must see your health care provider regularly.

Who should not take Trizivir?

Do not take Trizivir if you have ever had a serious allergic reaction (a hypersensitivity reaction) to any of the medicines that make up Trizivir, especially Ziagen (abacavir). If you have had such a reaction, return all of your unused Trizivir to your doctor or pharmacist.

Do not take Trizivir if you weigh less than 90 pounds.

How should I take Trizivir?

To help make sure that your anti-HIV therapy is as effective as possible, take your Trizivir exactly as your doctor prescribes it. Do not skip any doses.

The usual dosage is 1 tablet twice a day. You can take Trizivir with food or on an empty stomach.

If you miss a dose of Trizivir, take the missed dose right away. Then, take the next dose at the usual scheduled time. Do not let your Trizivir run out. The amount of virus in your blood may increase if your anti-HIV drugs are stopped, even for a short time. Also, the virus in your body may become harder to treat.

What should I avoid while taking Trizivir?

Do not take Epivir, Retrovir, Combivir®, or Ziagen while taking Trizivir. These medicines are already in Trizivir.

You should avoid taking stavudine (Zerit®) while taking Trizivir. If your doctor prescribes doxorubicin or ribavirin, tell your doctor that you are taking Trizivir.

Practice safe sex while using Trizivir. Do not use or share dirty needles. Trizivir does not reduce the risk of passing HIV to others through sexual contact or blood contamination.

Talk to your doctor if you are pregnant or if you become pregnant while taking Trizivir. Trizivir has not been studied in pregnant women. It is not known whether Trizivir will harm the unborn child.

Mothers with HIV should not breastfeed their babies because HIV is passed to the baby in breast milk. Also, Trizivir can be passed to babies in breast milk and could cause the child to have side effects.

What are the possible side effects of Trizivir?

Life-threatening allergic reaction. Trizivir contains abacavir, which is also called Ziagen. Abacavir has caused some people to have a life-threatening allergic reaction (hypersensitivity reaction) that can cause death. How to recognize a possible reaction and what to do are discussed in "What is the most important information I should know about Trizivir?" at the beginning of this Medication Guide.

Lactic acidosis and severe liver problems. The medicines in Trizivir can cause a serious condition called lactic acidosis and, in some cases, this condition can cause death. Nausea and tiredness that don't get better may be symptoms of lactic acidosis. Women are more likely than men to get this serious side effect.

Blood problems. Retrovir, one of the medicines in Trizivir, can cause serious blood cell problems. These include reduced numbers of white blood cells (neutropenia) and extremely reduced numbers of red blood cells (anemia). These blood cell problems are especially likely to happen in patients with advanced HIV disease or AIDS.

Your doctor should be checking your blood cell counts regularly while you are taking Trizivir. This is especially important if you have advanced HIV or AIDS. This is to make sure that any blood cell problems are found quickly.

Muscle weakness. Retrovir, one of the medicines in Trizivir, can cause muscle weakness. This can be a serious problem.

Other side effects. Trizivir can cause other side effects. The most common side effects of taking the medicines in Trizivir together are nausea, vomiting, diarrhea, loss of appetite, weakness or tiredness, headache, dizziness, pain or tingling of the hands or feet, and muscle and joint pain.

Changes in body fat have been seen in some patients taking antiretroviral therapy. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the trunk. Loss of fat from the legs, arms, and face may also happen. The cause and long-term health effects of these conditions are not known at this time.

This listing of side effects is not complete. Your doctor or pharmacist can discuss with you a more complete list of side effects with Trizivir.

Ask a health care professional about any concerns about Trizivir. If you want more information, ask your doctor or pharmacist for the labeling for Trizivir that was written for health care professionals.

Do not use Trizivir for a condition for which it was not prescribed. Do not give Trizivir to other persons.

GlaxoSmithKline
GlaxoSmithKline
Research Triangle Park, NC 27709

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This Medication Guide has been approved by the US Food and Drug Administration.

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ROCHE PHARMACEUTICALS

Roche Pharmaceuticals provides support for targeted AIDS-related community education, prevention, and outreach programs throughout the US. But our toughest battles are fought in the laboratory and the clinic. A leader in virology, we have been active in the search for better ways to diagnose and treat HIV/AIDS since the earliest days of the epidemic. And we're in the fight for good.

GLAXOSMITHKLINE

GlaxoSmithKline is a pharmaceutical industry leader in HIV research and therapies. In 1998, Glaxo Wellcome sponsored more than 180 clinical trials to better understand how currently marketed compounds benefit patients.

As a leader in the development of HIV therapies, GlaxoSmithKline is involved in numerous initiatives on the federal, state, and local levels that address issues of delivery of care for people infected with HIV.

In addition to their own extensive research program, the company is involved in numerous efforts to work with others involved in the development of new advances in HIV therapies, vaccines, and diagnostics. The company is an active participant in the Inter-Company Collaboration for AIDS Drug Development Group, a group of pharmaceutical companies formed in 1993 to facilitate early combination and comparative studies of antiviral agents for the treatment of HIV disease.

GlaxoSmithKline is a research-based company whose people are committed to fighting disease by bringing innovative medicine and services to patients throughout the world and the healthcare providers who serve them.

CVS PROCARE PHARMACY

ProCare Pharmacy is the nation's leading specialty pharmacy. ProCare is a full service pharmacy providing comprehensive pharmaceutical care to clients living with chronic, challenging health conditions, such as HIV and AIDS, transplantation, and conditions associated with fertility.

Clients are provided with personalized services from expert pharmacists, medications counseling, adherence monitoring, reimbursement counseling, and nationwide delivery. ProCare currently provides care to over 50,000 customers on a national basis.

For more information regarding ProCare call 800.238.7828.

ROCHE DIAGNOSTICS

Roche Diagnostics recently received marketing approval from the FDA for its Amplicor HIV-1 Monitor UltraSensitive Method. This test is now the most sensitive means to measure levels of HIV circulating in an infected person's blood ("viral load"). The test can measure levels previously considered "undetectable"—down to 50 copies per millimeter of plasma. The approval is considered a significant advance in the battle against HIV. Published studies indicate that lowering plasma HIV RNA to below 50 copies/mL is associated with a more complete and durable viral suppression. Physicians will now have a clearer picture of therapeutic effectiveness against the HIV virus. Ask your physician or healthcare provider about Amplicor UltraSensitive and Roche products and information.

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FROM THE EDITOR

Editorial: Rapid HIV Testing—Step Forward or Step Backward?

We live in a world of instant access. Information on demand. E-mail so rapid that it is almost incomprehensible to think of snail mail as the communication medium that we used to rely on so heavily.

As technology and medical science improve, they bring with them not only advances but also challenges. We are now faced with a rapid HIV test (OraQuick®, OraSure Technologies) that can deliver highly accurate results in as little as 20 minutes. This breakthrough is being hailed as a major step forward in getting people tested and not losing them to followup. This will be a tremendous asset to case finding.

However, we may also be taking a step backward. As a community, how are we going to deal with the stress and anxiety associated with that 20-minute wait? What kind of mental health interventions will work? What about the person who just drops in for testing "on a whim" and finds out he is positive? How do we plan on providing acute crisis support and care in situations like these?

I ran a testing site for a number of years. The anxiety I saw in people when I was about to give them their results was intense and often overwhelming.

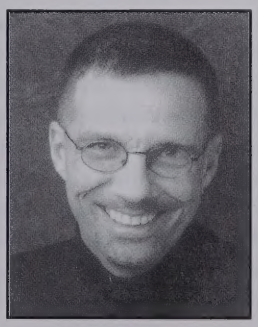
I also know what it is like to get a positive test result myself. I thought I was prepared for my positive result, but that was far from the reality that hit me. I was totally shocked, frightened, and in disbelief. I walked around numb for the next six months not knowing what I should do. Testing positive is always a traumatic event. Most people flounder and need time to adjust to their HIV status. Few people simply pick themselves up and brush themselves off and enter treatment. With rapid testing, we need to ensure that there will be follow-up and case management. We cannot let newly diagnosed people "fall through the cracks."

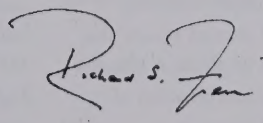
Even in the age of treatment advances, there is still that awful feeling connected with being newly diagnosed. There are no magic pills. Living with HIV can be downright exhausting.

An unsettling cloud is on the horizon. How are we going to approach women (many possibly in active labor) about getting the rapid test if they do not know their status? It is hard to believe that a woman about to give birth will be able to make an informed decision and not panic if she tests positive.

Guidelines are needed. We have to build on our past work in counseling and testing while taking a hard look at these issues. It is time to develop strategies that can be implemented and that actually work. Organizations that are going to do rapid HIV testing need to look at their programs, develop systems, and provide training to all involved case management and support staff. We must be proactive to prevent potential harm from being done.

I look forward to your comments and feedback.





Richard S Ferri, PhD, ANP, ACRN, FAAN
Managing Editor

Suggested Reading

Approval of a New Rapid Test for HIV Antibody. MMWR. 2002;51:1051–1052.

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The publishers, editors, contributors, and everyone involved in the publication of this periodical strive to bring to the public the most up-to-date, cutting-edge information concerning medical treatment, nutrition, and exercise regimens as such affect people living with HIV and AIDS. However, as with information on any course of treatment, but particularly as with the information contained herein that includes the newest information available, such is not, and is not intended to be, a substitute for professional medical advice. You should therefore not use this information to diagnose or treat a health problem or disease without consulting a qualified healthcare provider, familiar with your particular medical, treatment, and health situation. Before acting upon any of the information contained herein, you should consult your healthcare provider with any questions or concerns you may have concerning, or that may be raised by, the information herein.

News from the 10th Annual Conference on Retroviruses and Opportunistic Infections

BILL VALENTI, MD

The 10th Conference on Retroviruses and Opportunistic Infections was held from February 10 to 14, 2003 in Boston, Massachusetts. The chief presentations of the conference are summarized below.

Editor's note: All abstracts referenced in this article are taken from the Abstracts of the 10th Conference on Retroviruses and Opportunistic Infections. February 10–14, 2003. Boston, MA. The complete abstracts are available online at: www.retroconference.org.

PRESIDENT CLINTON'S KEYNOTE ADDRESS

Former President Clinton emphasized the global impact of the AIDS pandemic: 40 million are infected worldwide, with the highest death rate in those in their most productive years, leaving large gaps in the social and political structure of developing nations. While the global epidemic is currently centered in Africa, the fastest growth rates of HIV infection are in the former Soviet Union, India, and China. As he pointed out, "This is everybody's problem."

Progress is possible, but we must be aggressive in its pursuit. Eighteen states have proposed decreases in Medicaid funding, even though Medicaid provides 40 percent of HIV care. President Bush has proposed $3 billion in AIDS funding for Africa, but there is no guarantee that this money will be allocated by Congress.

Moreover, we must avoid simply throwing money at the problem, and instead ensure that we have systems in place to implement effective programs. Success will be a combination of scientific as well as political progress.

HIV INFECTIONS INCREASING

Valdiserri R. Preventing new HIV infections in the US: what can we hope to achieve? [Abstract 4]

Citing data from 25 states that report HIV diagnoses, CDC researchers noted an 8 percent increase in HIV diagnoses in the period from 1999 to 2001. But the fastest-growing sector of transmission in these 25 states is men who have sex with men (MSM), with an increase of 14 percent. Transmission through heterosexual activity increased by 10 percent, while injection drug use declined as a mode of transmission.

These 25 states represent only about a quarter of all US infections and do not include the high-incidence states of New York and California. So the data may not be representative. Also, the data represent new diagnoses and not necessarily new infections.

Medical providers can help by encouraging HIV testing and by discussing the need for patients to disclose their serostatus to sexual partners. A previous survey of patients at six public health clinics in California showed that men who have sex with men were half as likely to report discussions of safer sex with their providers as were heterosexual clients.

SEROCONVERSION IN DISCORDANT COUPLES

Wawer MJ, et al. HIV-1 transmission per coital act, by stage of HIV infection in the HIV-negative index partner, in discordant couples, Rakai, Uganda. [Abstract 40]

In a related presentation, research from the Rakai region of Uganda found that 48 percent of infections occurring in serodiscordant couples occurred within 5 months of the first partner becoming infected. The period of acute HIV infection is when viral load is especially high, before some degree of immune control establishes a viral set point. Participants agreed that similar patterns of infection are likely to occur in the US.

T-1249 EFFECTIVE AGAINST ENFUVIRTIDE-RESISTANT HIV

Miralles GD, et al. T-1249 demonstrates potent antiviral activity over 10-day dosing in most patients who have failed a regimen containing enfuvirtide: planned interim analysis of T1249-102, A Phase I/II study. [Abstract 14lb]

The investigational drug T-1249, a fusion inhibitor given subcutaneously, is a potent suppressor of plasma HIV RNA in patients who have developed viruses resistant to enfuvirtide (Fuzeon, Roche). T-1249 is in the same class as enfuvirtide, which has completed Phase III trials and has been shown to be effective in reducing HIV replication.

This study evaluated the short-term antiretroviral activity of T-1249 in 54 patients who failed an enfuvirtide regimen. Results of the interim analysis of the first 24 patients were presented.

Patients were HIV-1–infected adults participating in a Phase II or III enfuvirtide study who were receiving enfuvirtide and a stable background antiretroviral regimen. All patients demonstrated two consecutive plasma HIV RNA values between 5000 and 500,000 copies/mL. Patients were given 10 days of treatment along with the unchanged background regimen.

All 24 patients (96%) demonstrated enfuvirtide-resistance mutations and/or decreased phenotypic susceptibility to enfuvirtide and were included in the intent-to-treat population. No patient discontinued T-1249 prematurely. There were three adverse events, but none were serious and none were T-1249–related, according to the investigators. The median log10 HIV RNA change from baseline at day 11 was –1.12. Fifteen patients (63%) had at least a 1.0 log10 and 19 patients (79%) had at least a 0.5 log10 drop in HIV RNA at day 11.

The authors concluded that response appeared to be related to length of enfuvirtide therapy, with T-1249 demonstrating greatest potency in patients who had shorter enfuvirtide treatment: all patients who failed enfuvirtide for 24 to 48 weeks (7 patients) achieved at least a 1 log10 decrease in HIV RNA with median day 11 decrease in HIV RNA of –1.6 log10, while patients who failed enfuvirtide for more than 48

weeks achieved a median day 11 decrease in HIV RNA of –0.94 log10.

Editor's note: See discussion of enfuvirtide elsewhere in this issue.

TENOFOVIR: 96-WEEK DATA

Staszewski S, et al. Efficacy and safety of tenofovir DF (TDF) versus stavudine (D4t) when used in combination with lamivudine and efavirenz in antiretroviral-naïve patients: 96-week preliminary interim results. [Abstract 564b]

Study 903 is an ongoing 3-year, randomized, double-blind, Phase III trial designed to compare the efficacy and safety of a treatment regimen of tenofovir (Viread®, Gilead), lamivudine (3TC—Epivir®, GlaxoSmithKline) and efavirenz (Sustiva®, Bristol-Myers Squibb) to a regimen of stavudine, lamivudine, and efavirenz in 600 antiretroviral-naïve patients with HIV infection.

The tenofovir and stavudine arms reduced HIV RNA to <400 copies/mL in 82 percent and 78 percent of patients, respectively, using the most conservative "missing equals failure" analysis; 78 percent and 74 percent of patients, respectively, achieved HIV RNA less than 50 copies/mL. Patients in both arms of the study experienced substantial increases in mean CD4 cell counts, from the baseline mean of 276 to 537 cells/mm^3 in the tenofovir arm and from the baseline mean of 283 to 549 cells/mm^3 in the stavudine arm. Grade 3 and 4 adverse events and laboratory abnormalities were similar across treatment groups. There was a low discontinuation rate of approximately 15 percent in both arms.

Patients in the tenofovir arm had significantly better fasting triglycerides and cholesterol levels, weight gain, and physician-reported lipodystrophy. In a substudy of 250 patients, whole-body DEXA scans showed significantly more limb fat in the tenofovir arm than in the stavudine arm at 96 weeks.

Patients who received tenofovir had significantly fewer adverse events associated with mitochondrial toxicity, such as peripheral neuropathy, lactic acidosis, and lipodystrophy. After 96 weeks of treatment, the relative risk of these toxicities was 5.5 fold greater in the stavudine-containing arm compared with the tenofovir-containing arm.

Editor's Note: See discussion of tenofovir elsewhere in this issue.

IMMUNE-BASED THERAPIES

Harrer E, et al. Phase-I study with a therapeutic MVA-BN-Nef vaccine in HIV-1 infected patients on HAART. [Abstract 60]

Levy Y, et al. ANRS 093 Study Group. Immunological and virological efficacy of ALVAC-VIH 1433 and HIV lipopeptides (Lipo-6T) combined with SC IL-2 in chronically HIV-infected patients: results of the ANRS 093 randomized study. [Abstract 62]

Salmon D, et al. CD4+ and CD8+ T-cell responses are induced in chronically HIV-1 infected patients after immunization by a lipopeptide vaccine. [Abstract 643]

In a study by Harrer, et al., a modified vaccinia vector vaccine virally suppressed patients with CD4+ cell counts >400 cells/µL. The vaccine was not effective in preventing the virologic rebound following interruption of HAART, although lower HIV-1 RNA levels were noted compared to patients' pre-HAART levels. Patients who had stronger responses to the vaccine or the vector were more likely to delay re-initiation of HAART.

In another approach, Levy, et al. used dual lipopeptide vaccine plus interleukin-2 (IL-2). Seventy patients were randomized to receive either HAART alone or HAART plus the vaccines/IL-2. Of study participants, 91 percent stopped HAART after 40 weeks. Twelve weeks later, 5 percent of controls and 24 percent of vaccinated patients had viral loads <10,000 copies/mL and remained off HAART, as defined by the protocol. The time to virologic failure was significantly delayed in the vaccines/IL-2 arm.

Salmon described the induction of new CD4 and CD8 cell responses with the lipopeptide vaccine, but did not demonstrate improved virologic control.

NEW FDA APPROVED TREATMENTS FOR HEPATITIS C: PEGASYS® AND COPEGUS™

The US Food and Drug Administration approved Pegasys® (Roche) in 2002 and Copegus™ (Roche) in 2003 for the treatment of hepatitis C (HCV). Pegasys, an improved, pegylated form of interferon, is approved for use as monotherapy or with Copegus in patients with chronic HCV who have compensated liver disease and who have not previously been treated with interferon alfa. Pegylation allows the interferon to remain active in the bloodstream over a longer period of time than is the case with standard interferon alfa. Higher, more constant blood levels allow for weekly dosing intervals, compared to standard interferons. Most doctors are expected to use Pegasys in combination with Copegus, since clinical trials of hepatitis C monoinfection have demonstrated more sustained virologic responses (SVR) with combination therapy compared to interferon alone.

See Dr Valenti's bio on page 11. N

Recent Developments in HIV Medicine

BILL VALENTI, MD

Drug-Resitant HIV in Newly Infected Persons

Little SJ, Holte S, Roouty J-P, et al. Antiretroviral-drug resistance among patients recently infected with HIV. New Engl J Med. 2002;347:385–394.

Among persons in North America who are newly infected with HIV, the prevalence of transmitted resistance to antiretroviral drugs has been estimated at 1 to 11 percent. In a recently published study by Little et al., researchers determined the prevalence of such resistance in a retrospective analysis of susceptibility to antiretroviral drugs (phenotype testing) before treatment and drug-resistance mutations in HIV plasma samples (genotype testing) from 337 subjects with primary HIV infection who had not yet received treatment between May 1995 and June 2000 in ten North American cities. Responses to treatment could be evaluated in a subgroup of 202 subjects.

Over the 5-year period, the frequency of transmitted drug resistance increased significantly between two groups of patients divided according to date of diagnosis (1995–1998 and 1999–2000). The frequency of high-level resistance by phenotype testing to one or more drugs increased from 3.4 percent during 1995–1998 to 12.4 percent during 1999–2000, and the frequency of multidrug resistance increased from 1.1 percent to 6.2 percent, respectively. Among subjects with multidrug resistance, none identified before 1999 had so-called high-level resistance by phenotype for one or more drugs in all three antiretroviral classes, whereas 75 percent of subjects with multidrug resistance identified in 1999 or 2000 had high-level phenotype resistance to all three classes of antiretrovirals.

The frequency of resistance mutations detected by genotype testing increased from 8.0 percent during 1995–1998 to 22.7 percent during 1999–2000, and the frequency of multidrug resistance detected by genotype testing increased from 3.8 percent during 1995–1998 to 10.2 percent during 1999–2000.

Seventy-four percent of subjects received a regimen containing a protease inhibitor; 20 percent a regimen containing a non-nucleoside reverse transcriptase inhibitor; and 6 percent a regimen containing both. Among subjects infected with drug-resistant virus, the time to viral suppression after initiating antiretroviral therapy was longer, and the time to virologic failure was shorter.

The researchers concluded that the proportion of new HIV infections that involve drug-resistant virus is increasing in North America and that initial antiretroviral therapy is more likely to fail in patients who are infected with drug-resistant virus.

Editor's Note: The most significant conclusion was the authors' statement that testing for resistance to antiretroviral drugs before therapy begins is now indicated even for recently infected patients.

HIV Drugs During Pregnancy

Tuomala RE, Shapiro DE, Mofenson LM, et al. Antiretroviral therapy during pregnancy and the risk of an adverse outcome. N Eng J Med. 2002;346:1863–1870.

A recent study by Tuomala et al. of 3,266 HIV-infected expectant mothers found that those who took antiretrovirals were no more likely to give birth to premature or low–birth weight babies than those who did not. Comparing women treated with antiretrovirals with those who were not treated, rates of premature delivery (<37 weeks) were 16 percent and 17 percent, respectively. Rates of low birth weight (<2500 gms) were 16 percent in both groups, and rates of very low birth weight, low Apgar scores (<7), and still birth were low (<1%) and were similar in both groups.

The study did suggest an association between protease inhibitors and very low–birth weight babies. However, authors said that this finding, based on data on a small subset of women in the study, was not solid data and required further study. They commented that only the sickest women were treated with protease inhibitors, and that "the severity of the illness is likely to be responsible for the lower birth weight, as opposed to the drug itself."

The CDC estimates that 6,000 HIV-infected women give birth every year, and that 300 to 400 babies are born with the virus in the United States. One of the biggest public health successes of the AIDS epidemic has been the use of antiretroviral medicines to reduce HIV transmission from mothers to infants.

Editor's Note: The standard of care should continue to be treating HIV-infected expectant mothers as if they were not pregnant. The basis for this recommendation is that treatment of HIV is best for both mother and child. See the review of CDC guidelines for pregnant HIV-infected women elsewhere in this issue.

Nonoxynol-9 Update

Van Damme L, Vuylsteke B, Laga M, et al. Effectiveness of COL-1492, a nonoxynol-9 vaginal gel, on HIV-1 transmission in female sex workers: a randomised controlled trial. Lancet. 2002;360:971–977.

From 1996 until May 2000, UNAIDS sponsored a study of the effectiveness of a gel that contained 52.5 mg of nonoxynol-9 (N-9; COL-1492 in the trial and Advantage-S in the US; Columbia Laboratories) compared to an inactive placebo gel. Originally presented at the 13th International AIDS Conference in Durban, South Africa in 2000, the final report was published recently by Van Damme et al.

Nearly 1,000 HIV-negative female sex workers were enrolled in the trial, and all women were counseled to use condoms consistently and correctly. In addition to condom use, the women were asked to use a vaginal gel each time they had intercourse. Half of the women were provided a placebo gel, and half of the women received an N-9 gel. None of the women, or the researchers, knew which product each woman received.

At the end of the trial, researchers found that the women who used N-9 gel had become infected with HIV at about a 50 percent higher rate than women who used the placebo gel. Furthermore, the more frequently women used only N-9 gel (without a condom) to protect themselves, the higher their risk of becoming infected.

Shortly after the Durban conference, the US Centers for Disease Control issued an advisory stating that: (1) these adverse effects might not be seen at the same level among women who are using spermicides with N-9 less frequently or in different formulations; (2) given that N-9 has now been proven ineffective against HIV transmission, the possibility of risk, with no benefit, indicates that N-9 should not be recommended

NOW IN THE TREATMENT OF HEPATITIS C
A new day dawns
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Pharmaceuticals

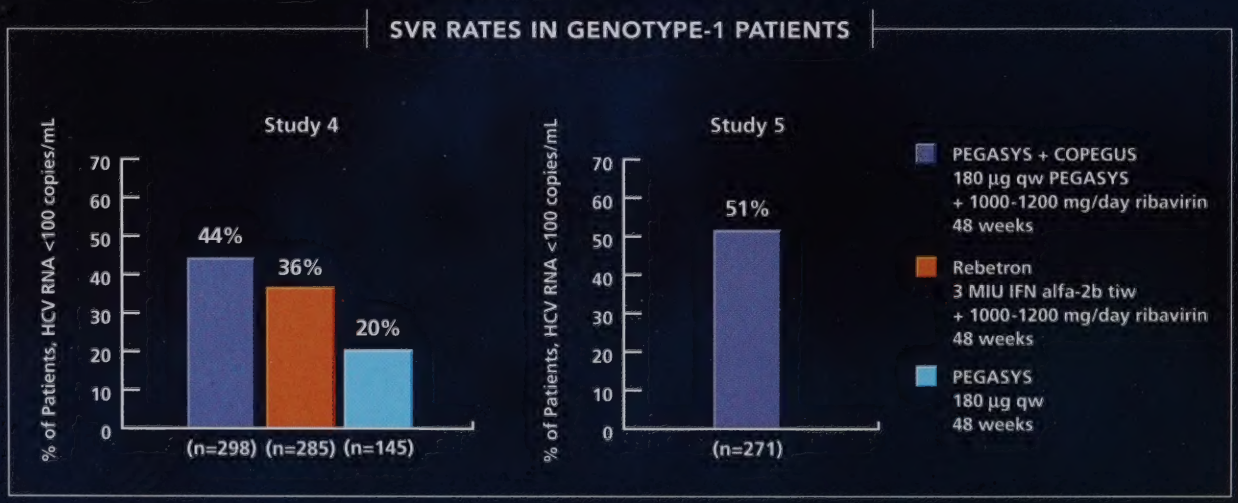
IN THE TREATMENT OF HEPATITIS C

Your needs haven't changed, your options have

Powerful efficacy...regardless of patient type

- In **two clinical trials,** more than half of all patients—53% of all patients in study 4 and 61% of all patients in study 5—achieved a sustained virologic response (SVR) on PEGASYS + COPEGUS combination therapy
- In genotype 2 and 3 patients, similar efficacy in less time with less ribavirin; 82% achieved an SVR following 24 weeks of PEGASYS + a low dose of COPEGUS (800 mg/day), compared with 76% of patients taking 48 weeks of PEGASYS + COPEGUS, regardless of COPEGUS dose (800,1000, or 1200 mg/day)

Genotype 1: Significant SVR rates in patients you treat most



Roche

Please see brief summary of complete product information for PEGASYS and COPEGUS on adjacent pages.

A treatment strategy tailored by genotype

DOSAGE RECOMMENDATIONS: COMBINATION THERAPY

Genotype	PEGASYS Dose	COPEGUS Dose	Duration
Genotype 1 or 4	180 µg qw	Patient weight: ≥75 kg=1200 mg <75 kg=1000 mg	48 weeks
Genotype 2 or 3	180 µg qw	800 mg	24 weeks

- As monotherapy, the recommended dose of PEGASYS is 180 µg qw for 48 weeks
- No dose adjustments with PEGASYS for patient weight

Sustained virologic response is defined as an undetectable HCV RNA value at the end of the treatment-free follow-up period (week 72).

Study design: In study 4, patients were randomized to receive either PEGASYS 180 µg qw with placebo, PEGASYS 180 µg qw with COPEGUS 1000 mg (body weight <75 kg) or 1200 mg (body weight ≥75 kg), or Rebetron® (interferon alfa-2b 3 MIU tiw plus 1000 mg or 1200 mg ribavirin) for 48 weeks of therapy followed by 24 weeks of treatment-free follow-up.

Study design: In study 5, all patients received PEGASYS 180 µg qw and were randomized to treatment for either 24 or 48 weeks and to a COPEGUS dose of either 800 mg or 1000 mg/1200 mg (for body weight <75 kg/≥75 kg).

NEW

PEGASYS® (Peginterferon alfa-2a) FOR INJECTION

COPEGUS™ (Ribavirin, USP) 200 MG TABLETS

Unleash the power of pegylation

For more information, call **1-877-PEGASYS (1-877-734-2797)** or log onto **www.pegasys.com.**

Alpha interferons, including PEGASYS (Peginterferon alfa-2a), may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Therapy should be withdrawn in patients with persistently severe or worsening signs or symptoms of these conditions. In many, but not all cases, these disorders resolve after stopping PEGASYS therapy (see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS and ADVERSE REACTIONS in complete product information).

Use with Ribavirin. Ribavirin, including COPEGUS™, may cause birth defects and/or death of the fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin causes hemolytic anemia. The anemia associated with ribavirin therapy may result in a worsening of cardiac disease. Ribavirin is genotoxic and mutagenic and should be considered a potential carcinogen (see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS and ADVERSE REACTIONS in complete product information).

PEGASYS, alone or in combination with COPEGUS, is indicated for the treatment of adults with chronic hepatitis C virus infection who have compensated liver disease and have not been previously treated with interferon alpha. Patients in whom efficacy was demonstrated included patients with compensated liver disease and histological evidence of cirrhosis (Child-Pugh class A).

PEGASYS is contraindicated in patients with hypersensitivity to PEGASYS or any of its components, autoimmune hepatitis, and decompensated hepatic disease (Child-Pugh class B and C) before or during treatment with PEGASYS. PEGASYS is also contraindicated in neonates and infants because it contains benzyl alcohol. Benzyl alcohol is associated with an increased incidence of neurological and other complications in neonates and infants, which are sometimes fatal. PEGASYS and COPEGUS therapy is additionally contraindicated in patients with a hypersensitivity to COPEGUS or any of its components, in women who are pregnant, men whose female partners are pregnant, and patients with hemoglobinopathies (eg, thalassemia major, sickle-cell anemia).

COPEGUS THERAPY SHOULD NOT BE STARTED UNLESS A REPORT OF A NEGATIVE PREGNANCY TEST HAS BEEN OBTAINED IMMEDIATELY PRIOR TO INITIATION OF THERAPY. Women of childbearing potential and men must use two forms of effective contraception during treatment and during the 6 months after treatment has concluded. Routine monthly pregnancy tests must be performed during this time. If pregnancy should occur during treatment or during 6 months post-therapy, the patient must be advised of the significant teratogenic risk of COPEGUS therapy to the fetus. Physicians and patients are also strongly encouraged to report any pregnancies that do occur to Roche by calling 1-800-526-6367.

The most common adverse events reported for PEGASYS and COPEGUS combination therapy observed in clinical trials (N=451) were fatigue/asthenia (65%), headache (43%), pyrexia (41%), myalgia (40%), irritability/anxiety/nervousness (33%), insomnia (30%), alopecia (28%), neutropenia (27%), nausea/vomiting (25%), rigors (25%), anorexia (24%), injection site reaction (23%), arthralgia (22%), depression (20%), pruritus (19%) and dermatitis (16%).

Serious adverse events included neuropsychiatric disorders (suicidal ideation and suicide attempt), serious and severe bacterial infections (sepsis), bone marrow toxicity (cytopenia and, rarely, aplastic anemia), cardiovascular disorders (hypertension, arrhythmias and myocardial infarction), hypersensitivity (including anaphylaxis), endocrine disorders (including thyroid disorders and diabetes mellitus), autoimmune disorders (including psoriasis and lupus), pulmonary disorders (dyspnea, pneumonia, bronchiolitis obliterans, interstitial pneumonitis and sarcoidosis), colitis (ulcerative and hemorrhagic/ischemic colitis), pancreatitis, and ophthalmologic disorders (decrease or loss of vision, retinopathy including macular edema and retinal thrombosis/hemorrhages, optic neuritis and papilledema).

NEW

PEGASYS®
(Peginterferon alfa-2a) FOR INJECTION

COPEGUS™
(Ribavirin, USP) 200 MG TABLETS

Unleash the power of pegylation

Please see brief summary of complete product information for PEGASYS and COPEGUS on adjacent pages.

Roche Pharmaceuticals

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PEGASYS®
(peginterferon alfa-2a)

Before prescribing, please consult the complete product information, a summary of which follows:

Alpha interferons, including PEGASYS (peginterferon alfa-2a), may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Therapy should be withdrawn in patients with persistently severe or worsening signs or symptoms of these conditions. In many, but not all cases, these disorders resolve after stopping PEGASYS therapy (see WARNINGS and ADVERSE REACTIONS).

Use with Ribavirin. Ribavirin, including COPEGUS™, may cause birth defects and/or death of the fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin causes hemolytic anemia. The anemia associated with ribavirin therapy may result in a worsening of cardiac disease. Ribavirin is genotoxic and mutagenic and should be considered a potential carcinogen (see COPEGUS Package Insert for additional information and other WARNINGS).

INDICATIONS AND USAGE
PEGASYS, peginterferon alfa-2a, alone or in combination with COPEGUS, is indicated for the treatment of adults with chronic hepatitis C virus infection who have compensated liver disease and have not been previously treated with interferon alpha. Patients in whom efficacy was demonstrated included patients with compensated liver disease and histological evidence of cirrhosis (Child-Pugh class A).

CONTRAINDICATIONS
PEGASYS is contraindicated in patients with:
- hypersensitivity to PEGASYS or any of its components
- autoimmune hepatitis
- hepatic decompensation (Child-Pugh class B and C) before or during treatment

PEGASYS is contraindicated in neonates and infants because it contains benzyl alcohol. Benzyl alcohol is associated with an increased incidence of neurologic and other complications in neonates and infants, which are sometimes fatal.

PEGASYS and COPEGUS combination therapy is additionally contraindicated in:
- Patients with known hypersensitivity to COPEGUS or to any component of the tablet.
- Women who are pregnant.
- Men whose female partners are pregnant.
- Patients with hemoglobinopathies (eg, thalassemia major, sickle-cell anemia).

WARNINGS
General
Patients should be monitored for the following serious conditions, some of which may become life threatening. Patients with persistently severe or worsening signs or symptoms should have their therapy withdrawn (see **BOXED WARNING**).

Neuropsychiatric
Life-threatening or fatal neuropsychiatric reactions may manifest in patients receiving therapy with PEGASYS and include suicide, suicidal ideation, depression, relapse of drug addiction, and drug overdose. These reactions may occur in patients with and without previous psychiatric illness.

PEGASYS should be used with extreme caution in patients who report a history of depression. Neuropsychiatric adverse events observed with alpha interferon treatment include aggressive behavior, psychoses, hallucinations, bipolar disorders, and mania. Physicians should monitor all patients for evidence of depression and other psychiatric symptoms. Patients should be advised to report any sign or symptom of depression or suicidal ideation to their prescribing physicians. In severe cases, therapy should be stopped immediately and psychiatric intervention instituted (see **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**).

Infections
Serious and severe bacterial infections, some fatal, have been observed in patients treated with alpha interferons including PEGASYS. Some of the infections have been associated with neutropenia. PEGASYS should be discontinued in patients who develop severe infections and appropriate antibiotic therapy instituted.

Bone Marrow Toxicity
PEGASYS suppresses bone marrow function and may result in severe cytopenias. Ribavirin may potentiate the neutropenia and lymphopenia induced by alpha interferons including PEGASYS. Very rarely alpha interferons may be associated with aplastic anemia. It is advised that complete blood counts (CBC) be obtained pre-treatment and monitored routinely during therapy (see **PRECAUTIONS: Laboratory Tests**).

PEGASYS and COPEGUS should be used with caution in patients with baseline neutrophil counts <1500 cells/mm^3, with baseline platelet counts <90,000 cells/mm^3 or baseline hemoglobin <10 g/dL. PEGASYS therapy should be discontinued, at least temporarily, in patients who develop severe decreases in neutrophil and/or platelet counts (see **DOSAGE AND ADMINISTRATION: Dose Modifications**).

Cardiovascular Disorders
Hypertension, supraventricular arrhythmias, chest pain, and myocardial infarction have been observed in patients treated with PEGASYS.

PEGASYS should be administered with caution to patients with pre-existing cardiac disease. Because cardiac disease may be worsened by ribavirin-induced anemia, patients with a history of significant or unstable cardiac disease should not use COPEGUS (see **WARNING: Anemia** and **COPEGUS Package Insert**).

Hypersensitivity
Severe acute hypersensitivity reactions (eg, urticaria, angioedema, bronchoconstriction, anaphylaxis) have been rarely observed during alpha interferon and ribavirin therapy. If such reaction occurs, therapy with PEGASYS and COPEGUS should be discontinued and appropriate medical therapy immediately instituted.

Endocrine Disorders
PEGASYS causes or aggravates hypothyroidism and hyperthyroidism. Hyperglycemia, hypoglycemia, and diabetes mellitus have been observed to develop in patients treated with PEGASYS. Patients with these conditions at baseline who cannot be effectively treated by medication should not begin PEGASYS therapy. Patients who develop these conditions during treatment and cannot be controlled with medication may require discontinuation of PEGASYS therapy.

Autoimmune Disorders
Development or exacerbation of autoimmune disorders including myositis, hepatitis, ITP, psoriasis, rheumatoid arthritis, interstitial nephritis, thyroiditis, and systemic lupus erythematosus have been reported in patients receiving alpha interferon. PEGASYS should be used with caution in patients with autoimmune disorders.

Pulmonary Disorders
Dyspnea, pulmonary infiltrates, pneumonia, bronchiolitis obliterans, interstitial pneumonitis and sarcoidosis, some resulting in respiratory failure and/or patient deaths, may be induced or aggravated by PEGASYS or alpha interferon therapy. Patients who develop persistent or unexplained pulmonary infiltrates or pulmonary function impairment should discontinue treatment with PEGASYS.

Colitis
Ulcerative, and hemorrhagic/ischemic colitis, sometimes fatal, have been observed within 12 weeks of starting alpha interferon treatment. Abdominal pain, bloody diarrhea, and fever are the typical manifestations of colitis. PEGASYS should be discontinued immediately if these symptoms develop. The colitis usually resolves within 1 to 3 weeks of discontinuation of alpha interferon.

Pancreatitis
Pancreatitis, sometimes fatal, has occurred during alpha interferon and ribavirin treatment. PEGASYS and COPEGUS should be suspended if symptoms or signs suggestive of pancreatitis are observed. PEGASYS and COPEGUS should be discontinued in patients diagnosed with pancreatitis.

Ophthalmologic Disorders
Decrease or loss of vision, retinopathy including macular edema, retinal artery or vein thrombosis, retinal hemorrhages and cotton wool spots, optic neuritis, and papilledema are induced or aggravated by treatment with PEGASYS or other alpha interferons. All patients should receive an eye examination at baseline. Patients with pre-existing ophthalmologic disorders (eg, diabetic or hypertensive retinopathy) should receive periodic ophthalmologic exams during interferon alpha treatment. Any patient who develops ocular symptoms should receive a prompt and complete eye examination. PEGASYS treatment should be discontinued in patients who develop new or worsening ophthalmologic disorders.

Use With Ribavirin (Also, see COPEGUS Package Insert.)
Ribavirin may cause birth defects and/or death of the exposed fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients taking PEGASYS and COPEGUS combination therapy. COPEGUS THERAPY SHOULD NOT BE STARTED UNLESS A REPORT OF A NEGATIVE PREGNANCY TEST HAS BEEN OBTAINED IMMEDIATELY PRIOR TO INITIATION OF THERAPY. Women of childbearing potential and men must use two forms of effective contraception during treatment and for at least six months after treatment has concluded. Routine monthly pregnancy tests must be performed during this time (see BOXED WARNING, CONTRAINDICATIONS, PRECAUTIONS: Information for Patients, and COPEGUS Package Insert).

Anemia
The primary toxicity of ribavirin is hemolytic anemia. Hemoglobin <10 g/dL was observed in approximately 13% of COPEGUS and PEGASYS treated patients in clinical trials (see **PRECAUTIONS: Laboratory Tests**). The anemia associated with COPEGUS occurs within 1 to 2 weeks of initiation of therapy with maximum drop in hemoglobin observed during the first eight weeks. BECAUSE THE INITIAL DROP IN HEMOGLOBIN MAY BE SIGNIFICANT, IT IS ADVISED THAT HEMOGLOBIN OR HEMATOCRIT BE OBTAINED PRE-TREATMENT AND AT WEEK 2 AND WEEK 4 OF THERAPY OR MORE FREQUENTLY IF CLINICALLY INDICATED. Patients should then be followed as clinically appropriate.

Fatal and nonfatal myocardial infarctions have been reported in patients with anemia caused by ribavirin. Patients should be assessed for underlying cardiac disease before initiation of ribavirin therapy. Patients with pre-existing cardiac disease should have electrocardiograms administered before treatment, and should be appropriately monitored during therapy. If there is any deterioration of cardiovascular status, therapy should be suspended or discontinued (see **DOSAGE AND ADMINISTRATION: COPEGUS Dose Modification Guidelines**). Because cardiac disease may be worsened by drug-induced anemia, patients with a history of significant or unstable cardiac disease should not use COPEGUS (see **COPEGUS Package Insert**).

Renal
It is recommended that renal function be evaluated in all patients started on COPEGUS. COPEGUS should not be administered to patients with creatinine clearance <50 mL/minute (see **CLINICAL PHARMACOLOGY: Special Populations** in complete product information).

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PRECAUTIONS
General
The safety and efficacy of PEGASYS alone or in combination with COPEGUS for the treatment of hepatitis C have not been established in:
- Patients who have failed other alpha interferon treatments
- Liver or other organ transplant recipients
- Patients co-infected with human immunodeficiency virus (HIV) or hepatitis B virus (HBV)

Renal Impairment
A 25% to 45% higher exposure to PEGASYS is seen in subjects undergoing hemodialysis. In patients with impaired renal function, signs and symptoms of interferon toxicity should be closely monitored. Doses of PEGASYS should be adjusted accordingly. PEGASYS should be used with caution in patients with creatinine clearance <50 mL/min (see **DOSAGE AND ADMINISTRATION: Dose Modifications**).

Information for Patients
Patients receiving PEGASYS alone or in combination with COPEGUS should be directed in its appropriate use, informed of the benefits and risks associated with treatment, and referred to the PEGASYS and, if applicable, COPEGUS (ribavirin) MEDICATION GUIDES.

PEGASYS and COPEGUS combination therapy must not be used by women who are pregnant or by men whose female partners are pregnant. COPEGUS therapy should not be initiated until a report of a negative pregnancy test has been obtained immediately before starting therapy. Female patients of childbearing potential and male patients with female partners of childbearing potential must be advised of the teratogenic/embryocidal risks and must be instructed to practice effective contraception during COPEGUS therapy and for 6 months post-therapy. Patients should be advised to notify the physician immediately in the event of a pregnancy (see **CONTRAINDICATIONS** and **WARNINGS**).

Women of childbearing potential and men must use two forms of effective contraception during treatment and during the 6 months after treatment has concluded; routine monthly pregnancy tests must be performed during this time (see **CONTRAINDICATIONS** and **COPEGUS Package Insert**).

If pregnancy does occur during treatment or during 6 months post-therapy, the patient must be advised of the significant teratogenic risk of COPEGUS therapy to the fetus. To monitor maternal-fetal outcomes of pregnant women exposed to COPEGUS, the COPEGUS Pregnancy Registry has been established. Physicians and patients are strongly encouraged to register by calling 1-800-526-6367.

Patients should be advised that laboratory evaluations are required before starting therapy and periodically thereafter (see **Laboratory Tests**). Patients should be instructed to remain well hydrated, especially during the initial stages of treatment. Patients should be advised to take COPEGUS with food.

Patients should be informed that it is not known if therapy with PEGASYS alone or in combination with COPEGUS will prevent transmission of HCV infection to others or prevent cirrhosis, liver failure or liver cancer that might result from HCV infection. Patients who develop dizziness, confusion, somnolence, and fatigue should be cautioned to avoid driving or operating machinery.

If home use is prescribed, a puncture-resistant container for the disposal of used needles and syringes should be supplied to the patients. Patients should be thoroughly instructed in the importance of proper disposal and cautioned against any reuse of any needles and syringes. The full container should be disposed of according to the directions provided by the physician (see **MEDICATION GUIDE**).

Laboratory Tests
Before beginning PEGASYS or PEGASYS and COPEGUS combination therapy, standard hematological and biochemical laboratory tests are recommended for all patients. Pregnancy screening for women of childbearing potential must be performed.

After initiation of therapy, hematological tests should be performed at 2 weeks and 4 weeks and biochemical tests should be performed at 4 weeks. Additional testing should be performed periodically during therapy. In the clinical studies, the CBC (including hemoglobin level and white blood cell and platelet counts) and chemistries (including liver function tests and uric acid) were measured at 1, 2, 4, 6, and 8, and then every 4 weeks or more frequently if abnormalities were found. Thyroid stimulating hormone (TSH) was measured every 12 weeks. Monthly pregnancy testing should be performed during combination therapy and for 6 months after discontinuing therapy.

The entrance criteria used for the clinical studies of PEGASYS may be considered as a guideline to acceptable baseline values for initiation of treatment:
- Platelet count ≥90,000 cells/mm^3 (as low as 75,000 cells/mm^3 in patients with cirrhosis)
- Caution should be exercised in initiating treatment in any patient with baseline risk of severe anemia (eg, spherocytosis, history of GI bleeding).
- Absolute neutrophil count (ANC) ≥1500 cells/mm^3
- Serum creatinine concentration <1.5 x upper limit of normal
- TSH and T_4 within normal limits or adequately controlled thyroid function

PEGASYS treatment was associated with decreases in WBC, ANC, lymphocytes, and platelet counts often starting within the first 2 weeks of treatment (see **ADVERSE REACTIONS**). Dose reduction is recommended in patients with hematologic abnormalities (see **DOSAGE AND ADMINISTRATION: Dose Modifications**).

While fever is commonly caused by PEGASYS therapy, other causes of persistent fever must be ruled out, particularly in patients with neutropenia (see **WARNINGS: Infections**).

Transient elevations in ALT (2-fold to 5-fold above baseline) were observed in some patients receiving PEGASYS, and were not associated with deterioration of other liver function tests. When the increase in ALT levels is progressive despite dose reduction or is accompanied by increased bilirubin, PEGASYS therapy should be discontinued (see **DOSAGE AND ADMINISTRATION: Dose Modifications**).

Drug Interactions
Treatment with PEGASYS once weekly for 4 weeks in healthy subjects was associated with an inhibition of P450 1A2 and a 25% increase in theophylline AUC. Theophylline serum levels should be monitored and appropriate dose adjustments considered for patients given both theophylline and PEGASYS (see **PRECAUTIONS**). There was no effect on the pharmacokinetics of representative drugs metabolized by CYP 2C9, CYP 2C19, CYP 2D6 or CYP 3A4. In patients with chronic hepatitis C treated with PEGASYS in combination with COPEGUS, PEGASYS treatment did not affect ribavirin distribution or clearance.

Nucleoside Analogues

Didanosine

Co-administration of COPEGUS and didanosine is not recommended. Reports of fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported in clinical trials (see **CLINICAL PHARMACOLOGY: Drug Interactions** in complete product information).

Stavudine and Zidovudine

Ribavirin can antagonize the in vitro antiviral activity of stavudine and zidovudine against HIV. Therefore, concomitant use of ribavirin with either of these drugs should be avoided.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis

PEGASYS has not been tested for its carcinogenic potential.

Mutagenesis

PEGASYS did not cause DNA damage when tested in the Ames bacterial mutagenicity assay and in the in vitro chromosomal aberration assay in human lymphocytes, either in the presence or absence of metabolic activation.

Use With Ribavirin

Ribavirin is genotoxic and mutagenic. The carcinogenic potential of ribavirin has not been fully determined. In a p53 (+/-) mouse carcinogenicity study at doses up to the maximum tolerated dose of 100 mg/kg/day ribavirin was not oncogenic. However, on a body surface area basis, this dose was 0.5 times maximum recommended human 24-hour dose of ribavirin. A study in rats to assess the carcinogenic potential of ribavirin is ongoing.

Mutagenesis (see **COPEGUS Package Insert**)

Impairment of Fertility

PEGASYS may impair fertility in women. Prolonged menstrual cycles and/or amenorrhea were observed in female cynomolgus monkeys given sc injections of 600 µg/kg/dose (7200 µg/m^2/dose) of PEGASYS every other day for one month, at approximately 180 times the recommended weekly human dose for a 60 kg person (based on body surface area). Menstrual cycle irregularities were accompanied by both a decrease and delay in the peak 17ß-estradiol and progesterone levels following administration of PEGASYS to female monkeys. A return to normal menstrual rhythm followed cessation of treatment. Every other day dosing with 100 µg/kg (1200 µg/m^2) PEGASYS (equivalent to approximately 30 times the recommended human dose) had no effects on cycle duration or reproductive hormone status.

The effects of PEGASYS on male fertility have not been studied. However, no adverse effects on fertility were observed in male Rhesus monkeys treated with non-pegylated interferon alfa-2a for 5 months at doses up to 25 x 10^6 IU/kg/day (see **COPEGUS Package Insert**).

Pregnancy
Pregnancy: Category C

PEGASYS has not been studied for its teratogenic effect. Non-pegylated interferon alfa-2a treatment of pregnant Rhesus monkeys at approximately 20 to 500 times the human weekly dose resulted in a statistically significant increase in abortions. No teratogenic effects were seen in the offspring delivered at term. PEGASYS should be assumed to have abortifacient potential. There are no adequate and well-controlled studies of PEGASYS in pregnant women. PEGASYS is to be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. PEGASYS is recommended for use in women of childbearing potential only when they are using effective contraception during therapy.

Pregnancy: Category X: Use With Ribavirin (see CONTRAINDICATIONS)

Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. COPEGUS therapy is contraindicated in women who are pregnant and in the male partners of women who are pregnant (see CONTRAINDICATIONS, WARNINGS, and COPEGUS Package Insert).

If pregnancy occurs in a patient or partner of a patient during treatment or during the 6 months after treatment cessation, such cases should be reported to the COPEGUS Pregnancy Registry at 1-800-526-6367.

Nursing Mothers
It is not known whether peginterferon or ribavirin or its components are excreted in human milk. The effect of orally ingested peginterferon or ribavirin from breast milk on the nursing infant has not been evaluated. Because of the potential for adverse reactions from the drugs in nursing infants, a decision must be made whether to discontinue nursing or discontinue PEGASYS and COPEGUS treatment.

Pediatric Use
The safety and effectiveness of PEGASYS, alone or in combination with COPEGUS in patients below the age of 18 years have not been established.

PEGASYS contains benzyl alcohol. Benzyl alcohol has been reported to be associated with an increased incidence of neurological and other complications in neonates and infants, which are sometimes fatal (see **CONTRAINDICATIONS**).

Geriatric Use

Younger patients have higher virologic response rates than older patients. Clinical studies of PEGASYS alone or in combination with COPEGUS did not include sufficient numbers of subjects aged 65 or over to determine whether they respond differently from younger subjects. Adverse reactions related to alpha interferons, such as CNS, cardiac, and systemic (eg, flu-like) effects may be more severe in the elderly and caution should be exercised in the use of PEGASYS in this population. PEGASYS and COPEGUS are excreted by the kidney, and the risk of toxic reactions to this therapy may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it may be useful to monitor renal function. PEGASYS should be used with caution in patients with creatinine clearance <50 mL/min and COPEGUS should not be administered to patients with creatinine clearance <50 mL/min.

ADVERSE REACTIONS

PEGASYS alone or in combination with COPEGUS causes a broad variety of serious adverse reactions (see **BOXED WARNING** and **WARNINGS**). In all studies, one or more serious adverse reactions occurred in 10% of patients receiving PEGASYS alone or in combination with COPEGUS.

The most common life-threatening or fatal events induced or aggravated by PEGASYS and COPEGUS were depression, suicide, relapse of drug abuse/overdose, and bacterial infections; each occurred at a frequency of <1%.

Nearly all patients in clinical trials experienced one or more adverse events. The most commonly reported adverse reactions were psychiatric reactions, including depression, irritability, anxiety, and flu-like symptoms such as fatigue, pyrexia, myalgia, headache, and rigors.

Overall 11% of patients receiving 48 weeks of therapy with PEGASYS either alone (7%) or in combination with COPEGUS (10%) discontinued therapy. The most common reasons for discontinuation of therapy were psychiatric, flu-like syndrome (eg, lethargy, fatigue, headache), dermatologic, and gastrointestinal disorders.

The most common reason for dose modification in patients receiving combination therapy was for laboratory abnormalities; neutropenia (20%) and thrombocytopenia (4%) for PEGASYS and anemia (22%) for COPEGUS.

PEGASYS dose was reduced in 12% of patients receiving 1000 mg to 1200 mg COPEGUS for 48 weeks and in 7% of patients receiving 800 mg COPEGUS for 24 weeks. COPEGUS dose was reduced in 21% of patients receiving 1000 mg to 1200 mg COPEGUS for 48 weeks and 12% in patients receiving 800 mg COPEGUS for 24 weeks.

Because clinical trials are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug. Also, the adverse event rates listed here may not predict the rates observed in a broader patient population in clinical practice.

Adverse Reactions Occurring in ≥5% of Patients in Hepatitis C Clinical Trials (Pooled Studies 1, 2, 3, and Study 4)

Body System	PEGASYS 180 µg 48 week†	ROFERON-A*†	PEGASYS 180 µg + 1000 mg or 1200 mg COPEGUS 48 week**	Intron A + 1000 mg or 1200 mg REBETOL® 48 week**
	N=559	N=554	N=451	N=443
	%	%	%	%
Application Site Disorders				
Injection site reaction	22	18	23	16
Endocrine Disorders				
Hypothyroidism	3	2	4	5
Flu-like Symptoms and Signs				
Fatigue/Asthenia	56	57	65	68
Pyrexia	37	41	41	55
Rigors	35	44	25	37
Pain	11	12	10	9
Gastrointestinal				
Nausea/Vomiting	24	33	25	29
Diarrhea	16	16	11	10
Abdominal pain	15	15	8	9
Dry mouth	6	3	4	7
Dyspepsia	<1	1	6	5
Hematologic‡				
Lymphopenia	3	5	14	12
Anemia	2	1	11	11
Neutropenia	21	8	27	8
Thrombocytopenia	5	2	5	<1
Metabolic and Nutritional				
Anorexia	17	17	24	26
Weight decrease	4	3	10	10
Musculoskeletal, Connective Tissue and Bone				
Myalgia	37	38	40	49
Arthralgia	28	29	22	23
Back pain	9	10	5	5
Neurological				
Headache	54	58	43	49
Dizziness (excluding vertigo)	16	12	14	14
Memory impairment	5	4	6	5
Psychiatric				
Irritability/Anxiety/ Nervousness	19	22	33	38
Insomnia	19	23	30	37
Depression	18	19	20	28
Concentration impairment	8	10	10	13
Mood alteration	3	2	5	6
Resistance Mechanism Disorders				
Overall	10	6	12	10
Respiratory, Thoracic and Mediastinal				
Dyspnea	4	2	13	14
Cough	4	3	10	7
Dyspnea exertional	<1	<1	4	7
Skin and Subcutaneous Tissue				
Alopecia	23	30	28	33
Pruritus	12	8	19	18
Dermatitis	8	3	16	13
Dry skin	4	3	10	13
Rash	5	4	8	5
Sweating increased	6	7	6	5
Eczema	1	1	5	4
Visual Disorders				
Vision blurred	4	2	5	2

†Pooled studies 1, 2, and 3
*Either 3 MIU or 6/3 MIU of ROFERON-A
**Study 4
‡Severe hematologic abnormalities

Patients treated for 24 weeks with PEGASYS and 800 mg COPEGUS were observed to have lower incidence of serious adverse events (3% vs 10%), Hgb <10 g/dL (3% vs 15%), dose modification of PEGASYS (30% vs 36%) and COPEGUS (19% vs 38%) and of withdrawal from treatment (5% vs 15%) compared to patients treated for 48 weeks with PEGASYS and 1000 mg or 1200 mg COPEGUS. On the other hand the overall incidence of adverse events appeared to be similar in the two treatment groups.

The most common serious adverse event (3%) was bacterial infection (eg, sepsis, osteomyelitis, endocarditis, pyelonephritis, pneumonia). Other SAEs occurred at a frequency of <1% and included: suicide, suicidal ideation, psychosis, aggression, anxiety, drug abuse and drug overdose, angina, hepatic dysfunction, fatty liver, cholangitis, arrhythmia, diabetes mellitus, autoimmune phenomena (eg, hyperthyroidism, hypothyroidism, sarcoidosis, systemic lupus erythematosus, rheumatoid arthritis), peripheral neuropathy, aplastic anemia, peptic ulcer, gastrointestinal bleeding, pancreatitis, colitis, corneal ulcer, pulmonary embolism, coma, myositis, and cerebral hemorrhage.

PEGASYS® (peginterferon alfa-2a)

Laboratory Test Values

Hemoglobin

The hemoglobin concentration decreased below 12 g/dL in 17% (median Hgb drop = 2.2 g/dL) of monotherapy and 52% (median Hgb drop = 3.7 g/dL) of combination therapy patients. Severe anemia (Hgb <10 g/dL) was encountered in 13% of patients receiving combination therapy and 2% of monotherapy recipients. Dose modification for anemia was required in 22% of ribavirin recipients treated for 48 weeks. Hemoglobin decreases in PEGASYS monotherapy were generally mild and did not require dose modification (see **DOSAGE AND ADMINISTRATION: Dose Modifications**).

Neutrophils

Decreases in neutrophil count below normal were observed in 95% of patients treated with PEGASYS either alone or in combination with COPEGUS. Severe potentially life-threatening neutropenia (ANC <0.5x10^9/L) occurred in approximately 5% of patients receiving PEGASYS either alone or in combination with COPEGUS. Seventeen percent of patients receiving PEGASYS monotherapy and 20% to 24% of patients receiving PEGASYS/COPEGUS combination therapy required modification of interferon dosage for neutropenia. Two percent of patients required permanent reductions of PEGASYS dosage and <1% required permanent discontinuation. Median neutrophil counts return to pre-treatment levels 4 weeks after cessation of therapy (see **DOSAGE AND ADMINISTRATION: Dose Modifications**).

Lymphocytes

Decreases in lymphocyte count are induced by interferon alpha therapy. Lymphopenia was observed during both monotherapy (86%) and combination therapy with PEGASYS and COPEGUS (94%). Severe lymphopenia (<0.5x10^9/L) occurred in approximately 5% of monotherapy patients and 14% of combination PEGASYS and COPEGUS therapy recipients. Dose adjustments were not required by protocol. Median lymphocyte counts return to pre-treatment levels after 4 to 12 weeks of the cessation of therapy. The clinical significance of the lymphopenia is not known.

Platelets

Platelet counts decreased in 52% of patients treated with PEGASYS alone (median drop 45% from baseline), 33% of patients receiving combination with COPEGUS (median drop 30% from baseline). Median platelet counts return to pre-treatment levels 4 weeks after the cessation of therapy.

Triglycerides

Triglyceride levels are elevated in patients receiving alfa interferon therapy and were elevated in the majority of patients participating in clinical studies receiving either PEGASYS alone or in combination with COPEGUS. Random levels higher ≥400 mg/dL were observed in about 20% of patients.

ALT Elevations

Less than 1% of patients experienced marked elevations (5- to 10-fold above baseline) in ALT levels during treatment. These transaminase elevations were on occasion associated with hyperbilirubinemia and were managed by dose reduction or discontinuation of study treatment. Liver function test abnormalities were generally transient. One case was attributed to autoimmune hepatitis, which persisted beyond study medication discontinuation (see **DOSAGE AND ADMINISTRATION: Dose Modifications**).

Thyroid Function

PEGASYS alone or in combination with COPEGUS was associated with the development of abnormalities in thyroid laboratory values, some with associated clinical manifestations. Hypothyroidism or hyperthyroidism requiring treatment, dose modification or discontinuation occurred in 4% and 1% of PEGASYS treated patients and 4% and 2% of PEGASYS and COPEGUS treated patients, respectively. Approximately half of the patients, who developed thyroid abnormalities during PEGASYS treatment, still had abnormalities during the follow-up period (see **PRECAUTIONS: Laboratory Tests**).

Immunogenicity

Nine percent (71/834) of patients treated with PEGASYS with or without COPEGUS developed binding antibodies to interferon alfa-2a, as assessed by an ELISA assay. Three percent of patients (25/835) receiving PEGASYS with or without COPEGUS, developed low-titer neutralizing antibodies (using an assay of a sensitivity of 100 INU/mL).

The clinical and pathological significance of the appearance of serum neutralizing antibodies is unknown. No apparent correlation of antibody development to clinical response or adverse events was observed. The percentage of patients whose test results were considered positive for antibodies is highly dependent on the sensitivity and specificity of the assays.

Additionally, the observed incidence of antibody positivity in these assays may be influenced by several factors including sample timing and handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to PEGASYS with the incidence of antibodies to these products may be misleading.

OVERDOSAGE

There is limited experience with overdosage. The maximum dose received by any patient was 7 times the intended dose of PEGASYS (180 µg/day for 7 days). There were no serious reactions attributed to overdosages. Weekly doses of up to 630 µg have been administered to patients with cancer. Dose-limiting toxicities were fatigue, elevated liver enzymes, neutropenia, and thrombocytopenia. There is no specific antidote for PEGASYS. Hemodialysis and peritoneal dialysis are not effective.

DOSAGE AND ADMINISTRATION

There are no safety and efficacy data on treatment for longer than 48 weeks. Consideration should be given to discontinuing therapy after 12 to 24 weeks of therapy if the patient has failed to demonstrate an early virologic response (see **CLINICAL STUDIES** in complete product information).

PEGASYS

The recommended dose of PEGASYS monotherapy is 180 µg (1.0 mL) once weekly for 48 weeks by subcutaneous administration in the abdomen or thigh.

PEGASYS and COPEGUS COMBINATION

The recommended dose of PEGASYS when used in combination with ribavirin is 180 µg (1.0 mL) once weekly. The recommended dose of COPEGUS and duration for PEGASYS/COPEGUS therapy is based on viral genotype (see table below).

The daily dose of COPEGUS is 800 mg to 1200 mg administered orally in two divided doses. The dose should be individualized to the patient depending on baseline disease characteristics (eg, genotype), response to therapy, and tolerability of the regimen.

Since COPEGUS absorption increases when administered with a meal, patients are advised to take COPEGUS with food.

PEGASYS and COPEGUS Dosing Recommendations

Genotype	PEGASYS Dose	COPEGUS Dose	Duration
Genotype 1, 4	180 µg	<75 kg = 1000 mg ≥75 kg = 1200 mg	48 weeks 48 weeks
Genotype 2, 3	180 µg	800 mg	24 weeks

Genotypes 2 & 3 showed no increased response to treatment beyond 24 weeks.
Data on genotypes 5 and 6 are insufficient for dosing recommendations.

A patient should self-inject PEGASYS only if the physician determines that it is appropriate and the patient agrees to medical follow-up as necessary and training in proper injection technique has been provided to him/her (see illustrated PEGASYS **MEDICATION GUIDE** for directions on injection site preparation and injection instructions).

PEGASYS should be inspected visually for particulate matter and discoloration before administration, and not used if particulate matter is visible or product is discolored. Vials with particulate matter or discoloration should be returned to the pharmacist.

Dose Modifications

If severe adverse reactions or laboratory abnormalities develop during combination COPEGUS/PEGASYS therapy, the dose should be modified or discontinued, if appropriate, until the adverse reactions abate. If intolerance persists after dose adjustment, COPEGUS/PEGASYS therapy should be discontinued.

HOW SUPPLIED

Single Dose Vial

Each PEGASYS (peginterferon alfa-2a) 180 µg single use, clear glass vial provides 1.0 mL containing 180 µg peginterferon alfa-2a for sc injection. Each package contains 1 vial (NDC 0004-0350-09).

Monthly Convenience Pack

Four vials of PEGASYS (peginterferon alfa-2a), 180 µg single use, in a box with 4 syringes and 8 alcohol swabs (NDC 0004-0350-39). Each syringe is a 1 mL (1 cc) volume syringe supplied with a 27 gauge, ½ inch needle with needle-stick protection device.

Storage

Store in the refrigerator at 36° to 46°F (2° to 8°C). Do not freeze or shake. Protect from light. Vials are for single use only. Discard any unused portion.

Rx only

Roche Pharmaceuticals

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199
www.rocheusa.com

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as an effective means of HIV prevention; and (3) prevention messages that counsel individuals who can't use a condom to consider spermicides with N-9 for HIV prevention should immediately be revised. More information can be obtained at:
www.cdc.gov/hiv/pubs/mmwr/mmwr11aug00.htm and
www.cdc.gov/mmwr/preview/mmwrhtml/mm4931a4.htm.

Interim Analysis of ACTG 5059

The Food and Drug Administration (FDA) recently sent out a "Dear Provider" letter concerning the ACTG 5059 study. In the letter, the FDA stated that it had halted one arm of the study due to underperformance of Trizivir™ (AZT/3TC/abacavir, GlaxoSmithKline). This three-arm study randomized antiretroviral-naïve people to either (a) Trizivir only, (b) Combivir® (AZT/3TC, GlaxoSmithKline) plus Sustiva® (efavirenz, Bristol-Myers Squibb), or (c) all four drugs. The study was double blinded, and all participants took two pills in the morning and five pills at night. Viral loads of any level were allowed at entry.

The Trizivir-only arm underperformed with people experiencing virologic failure more rapidly than in the other treatment arms.

This data is certainly interesting, but it is important to remember that it has not been peer-reviewed or published. The interim data analysis needs further study. Clinicians and patients should be aware of these preliminary results when making treatment decisions involving any of the above listed antiretroviral combinations. As always, preliminary information like this needs to be put into context as a part of individualized patient decisions.

Bill Valenti, MD is the Founding Medical Director of the Community Health Network, a community-based medical clinic for HIV/AIDS in Rochester, NY, where he continues to see patients. He is Clinical Associate Professor of Medicine at the University of Rochester School of Medicine and Dentistry and has been involved in HIV care, policy, and program development since 1981.

MEDICINE Websites

GOVERNMENT

AIDS info
www.aidsinfo.nih.gov

Canada HIV Trials Network
www.hivnet.ubc.ca/ctn.html

CDC Division of HIV/AIDS Prevention
www.cdc.gov/hiv/dhap.htm

FDA Office of Special Health Issues
www.fda.gov/oashi/aids/hiv.html

NIH HIV/AIDS Information Service
www.sis.nlm.nih.gov/aids/index.html

NIH Office of AIDS Research
www.nih.gov/od/oar

ORGANIZATIONS

American Academy of Family Physicians
www.aafp.org

American Council of Science and Health
www.acsh.org

American Federation for Medical Research
www.afmr.org

American Medical Association
www.ama-assn.org

Association of Nurses in AIDS Care
www.anacnet.org

Gay and Lesbian Medical Association
www.glma.org

HIV Dentistry
www.hivdent.org

International Association of Physicians in AIDS Care
www.iapac.org

UNAIDS
www.unaids.org

World Health Organization (WHO)
www.who.int/hiv/en

EDUCATION

Brown University TB/HIV Research Laboratory
http://tbhiv.biomed.brown.edu/website/

Harvard AIDS Institute
www.hsph.harvard.edu/organizations/hai

Johns Hopkins AIDS Service
www.hopkins-aids.edu

US Pharmacopoeia
www.usp.org

JOURNALS/PUBLICATIONS

AIDS Treatment News
http://4.17.177.49/immunet/atn.nsf/homepage

AIDS Weekly Plus
www.newsfile.com/x1a.htm

Annals of Internal Medicine
www.acponline.org/journals/annals/annaltoc.htm

British Medical Journal
www.bmj.com/index.html

Cell
www.cell.com

Infectious Disease News
www.slackinc.com/general/idn/idnhome.htm

Journal of the American Medical Association (JAMA)
www.ama-assn.org/special/hiv

Journal of Infectious Disease
www.journals.uchicago.edu/jid

Lancet
www.thelancet.com

Merck Manual of Medical Information–Home Edition
www.merck.com/pubs/mmanual_home

MMWR–CDC
www2.cdc.gov/mmwr

Nature
www.nature.com

Nature Medicine
www.medicine.nature.com/content

The New England Journal of Medicine
www.nejm.org

Pharmacy News Magazine for Pharmacists
www.drugtopics.com

Science
http://science-mag.aaas.org/science

DATABASES

AIDS.org
www.aids.org/immunet/home.nsf/page/homepage

AEGIS
www.aegis.com

CDC National AIDS Clearinghouse
www.cdcnpin.org

Critical Path
www.critpath.org

Doctor's Guide AIDS Information Resources
www.pslgroup.com/aids.htm

HIV Database at Los Alamos
http://hiv-web.lanl.gov

HIV Medication Guide
www.jag.on.ca/hiv

Medline Plus
www.nlm.nih.gov

National Center for Health Statistics
www.cdc.gov/nchswww/default.htm

The Grateful Med
http://igm.nlm.nih.gov

The Body
www.thebody.com

The Combined Health Information Database (CHID)
http://chid.nih.gov

CONSULTATION

MD Consult
www.mdconsult.com

GLOSSARY

General Health Medical Glossary
www.ama-assn.org/insight /gen_hlth/glossary/index.htm

MULTIMEDIA

Animation of HIV Lifecycle
www.roche-hiv.com/search/ section_frame.html

HIV and Nutritional Care of the Incarcerated

BARBARA WAKEEN, MA, RD, LDAS, AA, DTR

HIV-positive inmates have different nutritional needs than their HIV-negative peers. Although the exact number of inmates with HIV/AIDS is unknown due to privacy and confidentiality issues, most are unidentified. This makes it more difficult for HIV-positive inmates to obtain the nutrients they need.

Most HIV-positive inmates, however, remain unidentified and are reluctant to come forward.[1] To decrease the risk of discrimination and possible abuse from other inmates, HIV-positive inmates may require segregation from the general population when signs of advanced disease are more apparent.

The physical and nutritional status of HIV-positive individuals diminishes as the disease state progresses.[2–5] Upon diagnosis, achieving and/or maintaining optimal nutritional status by means of a healthy diet is the first step in supporting the immune system with nutrition therapy.[6–9]

The information in this article comes from the results of a survey completed by corrections dietitians. A 2001 survey of American and Canadian dietitians working in corrections facilities was conducted to assess the nutrition support and treatment within food service operations of HIV-positive inmates. These corrections dietitians provide services for more than 315 establishments ranging from federal, state, and private prisons to detention facilities, work camps, and facilities for youthful offenders. The dietitians who completed the survey (n = 98) work in all types of correctional settings, and provide nutritional and food service expertise to one or more facilities.

Since the medical staff delivers most nutritional counseling in the correctional setting, dietitians are often unaware of an inmate's HIV status. Of the 98 dietitians surveyed, only 18 reported that they were aware of the HIV-positive status of inmates.

Eating foods on the general inmate population menu is encouraged while the inmate still has an appetite and can tolerate regular food. Computerized nutritional analysis showed that the average calorie and protein content provided by main population menus (2,400–3,700 calories/58–150 grams of protein for males; 2,200–3,200 calories/40–125 grams of protein for females) meets the nutrition guidelines established by the Association of Nutrition Services Agencies (formerly the AIDS Nutrition Services Alliance, or ANSA; www.aidsnutrition.org). Optimally, menus achieve the Recommended Dietary Allowances (RDA) and any additional meal patterns and standards required by their governing agency.

Poor diet has been associated with aggressive, antisocial, or violent behavior. Preliminary studies show that dietary supplements of vitamins, minerals, and omega 3 fatty acids may decrease the number of disciplinary offenses by young incarcerated adults.[10] Often vitamin and mineral supplements are ordered for HIV-positive inmates. Even when menus meeting RDA requirements are provided, inmate food intake may still be below RDA standards for many nutrients. Although some HIV-positive inmates get more calories and nutrients through special foods, supplemental feedings, and/or nutritional drinks, these nutrition therapy items are often traded or sold.

Commissaries or canteens are "convenience stores" within the correctional facility where inmates can purchase food items and nonfood items. Many of the foods available for sale are high in sodium, fat, and/or refined sugar. Some facilities do offer limited "healthier" low-fat and low-sugar items, but they are not the most popular choices.

According to the survey, food items that are currently unavailable to inmates but would be of benefit include sugar-free, reduced-sodium, and low-fat items for those on medical diets. Healthier canteen choices and allowing families to bring items such as multivitamins would also be beneficial. All inmates would benefit from high-fiber items, fresh fruits, and fresh vegetables. Nevertheless, although menu choices are often limited to a cycle menu and commissary offerings can lack valuable nutrients, these menus still meet RDA standards. The food offered may still allow some inmates to eat better than they did before incarceration.

Survey results disclosed that nutritional counseling efforts range from no counseling whatsoever to monthly instruction during a medical visit. Overall, whereas the *medical* treatment of HIV-positive inmates is similar in most corrections settings, specific treatment plans vary per agency and institution for *nutrition* therapy. Nutritional services that would benefit these inmates include not only dietitian consultations, but patient education using a multidisciplinary approach that is provided by dietitians and nurses, and not just by physicians.

With regard to food service in all facilities, HIV-positive inmates can hold jobs in the kitchen as long as they have the medical clearance to do so. In general, the survey indicated that correctional facilities do not permit individuals with AIDS and active infectious diseases, i.e., tuberculosis and hepatitis, to work in the food service department.

Nutritional services are an important part of health care. As with all HIV-positive people, inmates could benefit from learning about general nutrition and why good nutrition is important in HIV/AIDS. Education about nutrition can help people understand why they need to eat well.

Barbara Wakeen, MA, RD, LD, owns and operates Correctional Nutrition Consultants specializing in the provision of food service and nutritional consultation to jails and prisons, food processors, and food distributors across the US. She has more than 13 years of correctional food and nutrition experience and is the editor of the 2001 Correctional Food Service and Nutrition Manual. *She can be reached at:* bwakeen@neo.rr.com. N

For additional information on HIV and the incarcerated, visit:
www.thebody.com/tpan/julaug_01/incarcerated_women.html
www.nicic.org/pubs/2002/017477.pdf
www.corrections.com/

References

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NUTRITION Websites

GOVERNMENT

Department of Agriculture Center for Nutrition Policy and Promotion
www.usda.gov/cnpp

Food and Drug Administration
www.fda.gov

FDA Center for Food Safety and Applied Nutrition
vm.cfsan.fda.gov

National Agricultural Library
www.nal.usda.gov

Nutrient Information Statements
www.asns.org/

Office of Dietary Supplements
http://dietary-supplements.info.nih.gov/

ORGANIZATIONS

American Dietetic Association
www.eatright.org

American Society of Clinical Nutrition
www.faseb.org/ascn

American Society for Parenteral and Enteral Nutrition
www.clinnutr.org

British Dietetic Association Home Page
www.bda.uk.com/

Dietitians of Canada
www.dietitians.ca/

Food and Nutrition Alliance
www.faseb.org/ascn/fansapr.htm

HIV/AIDS Dietetic Practice Group
www.hivaidsdpg.org/

HIV Resources, Inc.
www.hivresources.com

International Food Information Council Foundation
www.ific.org/

EDUCATION

American College of Nutrition
www.am-coll-nutr.org

Cornell Cooperative Extension Food and Nutrition
www.cce.cornell.edu/food/

Oregon State University Food Resource
www.orst.edu/food-resource/ food.html

Professional Resources in Nutrition Sciences
www.academic.brooklyn.cuny.edu/hns/prins/

University of Toronto Department of Nutritional Sciences
www.utoronto.ca/nutrisci/

Washington State University Consumer Food Safety Resource Page
www.foodsafety.wsu.edu/

Tufts University Nutrition and HIV Research
www.tufts.edu/med/research/nutrition_hiv/main.htm

JOURNALS/PUBLICATIONS

Always Your Choice Nutrition Topics
www.alwaysyourchoice.com/diet_disease.html

The American Journal of Clinical Nutrition
www.ajcn.org

Food Resource
www.orst.edu/food-resource/food.html

HIV ReSource Review Nutrition Abstracts
www.hivresources.com/

Journal of the American College of Nutrition
www.am-coll-nutr.org/jacn/jacn.htm

Journal of Nutrition
www.nutrition.org

Journal of Parenteral and Enteral Nutrition Abstracts
www.clinnutr.org/

Nutrition Action Health Letter
www.cspinet.org/nah/index.htm

Organization for Nutrition Education
www.stfx.ca/academic/human-nutrition/organization/html

DATABASES

Blonz Guide Nutrition, Food, and Health Resources
www.blonz.com

Healthfinder
www.healthfinder.gov

International Bibliographic
www.odp.od.nih.gov/ods/databases/ibids.html

Mayo Clinic Nutrition Center
www.mayohealth.org/

Nutrition Navigator
www.navigator.tufts.edu

AUDIO

National Public Radio Dietary Supplement Series and Survey
www.npr.org/programs/morning/dietsupplements.html

SPECIAL DIETARY NEEDS

Information for Various Conditions
www.hivresources.com/

NIH Osteoporosis and Related Bone Diseases–National Resource Center
www.osteo.org/

FOOD GUIDE PYRAMIDS

Ethnic Cultural Food Guide Pyramids
www.nal.usda.gov/

American Food Guide Pyramid
www.nal.usda.gov:8001/

Kid's Pyramid
www.eatright.org/

Canada's Food Guide to Healthy Eating
www.canadianliving.com/

Healthy Eating Pyramids
www.oldwayspt.org

MISCELLANEOUS NUTRITION INFORMATION

Exercise and Nutrition Information
www.hivfitness.org

Information on Supplements
www.hivresources.com/

Nutrición y Recursos del VIH
www.hivresources.com/

Nutrition Links and Resources
www.hivresources.com/

Phytochemicals at Work
www.nutritionresource.com/

Targeting More Effective Exercise

MARY JANE DETROYER, MS, RD, CDN

Many people start a regular exercise program to improve health and to deal with complications associated with HIV infection. Let's say you've been exercising for a while and are not seeing the results you expected. This can be very frustrating and is actually one of the top reasons people stop exercising. Let's examine why your exercise program might not be effective and what you can do about it.

Inadequate Muscle Hypertrophy Response

Many men and women living with HIV experience unplanned weight loss and muscle wasting.[1,2,3] Poor food intake is a major reason for weight loss,[4] and high calorie diets that include supplements and appetite stimulants may be needed for weight gain. However, it is important to note that the gain is primarily fat and not muscle.[5] Other solutions, along with calorie replacement, may provide a more successful formula for building muscle.

Androgen deficiency is common among men and women with HIV infection.[6] HIV+ women often have free testosterone (the "unbound" hormone) levels below the age-adjusted normal range, with the lowest levels being found in the most severe cases of wasting.[7]

Before the advent of highly active antiretroviral therapy (HAART), 50 percent of men with AIDS wasting were reported to be hypogonadal. More recently, it was found that 21 percent of men with AIDS wasting who were receiving HAART still experienced hypogonadism.[8] Signs of testosterone deficiency include decreased libido, depression, and fatigue; testosterone deficiency is also associated with increased fat, decreased muscle, and decreased bone mass. Testosterone replacement can significantly increase weight and lean mass in men with low levels of this hormone.[6,9,10]

Depression and low energy can make it difficult to get off the sofa and out the door to exercise. Testosterone replacement can help relieve depression and increase muscle enough to increase energy and strength.[11] With additional energy, you should be able to get to the gym and work harder, which should result in greater muscle hypertrophy.[12]

Testosterone therapy is not always needed to build muscle mass in people with AIDS wasting who have normal levels of the hormone. Exercise alone has been documented to work just as effectively as testosterone in building muscle[13,14]; moreover, testosterone therapy can sometimes lower levels of cardio-protective high-density lipoprotein (HDL)—"the good cholesterol."[14] Make sure your testosterone levels are normal to ensure an appropriate muscle hypertrophy response to exercise.

Progressive resistance exercise (PRT) has been used to make significant gains in muscle mass in people living with HIV.[13,15] And PRT seems to be most effective in those with AIDS wasting. Because adding an anabolic agent like nandrolone decanoate or oxandralone to the PRT produces a synergistic effect that results in significantly greater gains in muscle, it may be helpful in some situations.[16,17]

Testosterone, Bone Density and Exercise

Accelerated bone mineral loss and reduced bone density have been found in both men and women who are deficient in testosterone.[18,19] Testosterone replacement has been shown to decrease biomarkers, like *N*–telepeptide, that are measures of bone resorption (breaking down of bone).[20] Testosterone replacement has also been shown to increase serum plasma 1,25–dihydroxyvitamin D (a hormone that aids in calcium absorption) and to increase calcium absorption.[21] Testosterone given to hypogonadal men raises bone density regardless of age[19] and increases both strength and muscle mass.[19,22]

Testosterone has been found to be more effective in increasing hip and lumbar spine bone density in eugonadal men with AIDS wasting compared with age-matched noninfected healthy controls.[23] It has been suggested that women with AIDS wasting and androgen deficiency might also benefit from testosterone's ability to build bone and muscle tissue.[18]

How You Exercise Matters

You can go to the gym every day and spend hours exercising, but if you perform the exercises incorrectly or choose a type of exercise not specific to your goal, you will be unsuccessful. Aerobic exercise improves heart and lung function and is most effective for fat loss. Resistance exercise is effective in increasing strength and muscle mass. This general prescription holds true for people with HIV infection.[24,25]

Moderate levels of exercise tend to boost immunity, whereas prolonged, intense exercise tends to suppress immune function. Therefore, moderate exercise is more favorable for individuals with HIV.[26,27] However, some research has found a similar positive effect on immune cells following intense and moderate exercise.[28] Your current fitness and activity level should determine your safe exercise intensity. If your fitness level is high and you can safely sustain intense workouts, take extra precaution to avoid exposure to germs for several hours following exercise when your immunity is most suppressed.

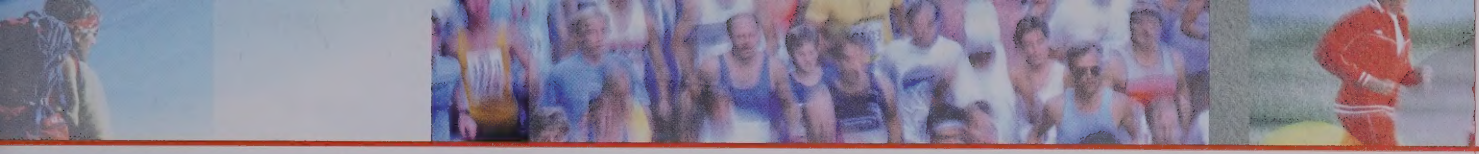
Progressive resistance training, using heavy weights, is very effective in building muscle in people with HIV infection and wasting. This type of weight training begins by determining the heaviest weight you can lift one time (1 RM). That number is multiplied by 80 percent, and the resulting number is the weight you start lifting with. This calculation should be done for each exercise you perform (back, chest, triceps, etc.). Every few weeks, you reassess your 1 RM weight, which should increase in response to training, and then take 80 percent of that new weight. Thus you will be progressively increasing the resistance as you train. Neglecting to increase your training weight at some point will prevent your muscle from growing. If this training concept seems confusing, seek out an exercise physiologist or personal trainer who can explain this concept to you, show you how to apply it to your workouts, and observe you to make sure you are performing the exercise correctly so as to avoid injury.

Target the large muscle groups—the legs, buttocks, chest, and back—to see the largest gains in muscle and body cell mass (BCM). Resist spending too much time on the vanity muscles—shoulders, triceps, and biceps—because exercising these muscles will not have as significant an impact on increasing BCM.

Supplements

The use of β-hydroxy-β-methylbutyrate (HMB), a metabolite of the amino acid leucine, as well as the amino acids L-arginine and L-glutamine has been shown to slow the breakdown of muscle protein. L-glutamine is synthesized primarily in skeletal muscle and is used by immune system, kidney, liver, and gastrointestinal tract tissues. During chronic inflammation and stress, the body uses glutamine at a faster rate than skeletal muscle can produce it. This results in decreased blood and muscle glutamine levels and a continuous breakdown of muscle tissue to supply the increased demand. Forty grams/day of L-glutamine plus antioxidants administered along with nutritional counseling to men and women with AIDS with a weight loss of greater than 5 percent improved BCM by 1.8 gm.[29]

HMB (1.5 gm), glutamine (7 gm), and arginine (7 gm) were combined in a dietary supplement mix to see whether they would have a synergistic effect on slowing muscle wasting in AIDS. In this randomized, placebo-controlled study,



participants who drank the supplement twice daily for 8 weeks gained 6.6 lbs, most of which, 5.6 lbs, was lean mass.[30]

If you are having difficulty eating enough calories to gain weight, or if the weight you are gaining is not muscle, discuss the option of taking one of these supplements with a registered dietitian. Investigate whether your insurance provider will pay for the supplement if the dietitian recommends a prescription from your doctor.

Tracking Your Progress

Bioelectrical Impedance Analysis (BIA) is the preferred method to follow in assessing changes in body composition—especially when tracking muscle wasting.

It makes sense to get a baseline BIA to determine what percentage of your weight is BCM and what is fat mass. Followup measurements should be done to assess the effectiveness of your nutrition plan, exercise regimen, and drug therapies. If you are not responding positively to exercise, strategies can be discussed with your healthcare providers to modify any element of your health care that might be impeding your ability to impact muscle growth.

Check List

Below is a checklist of the factors mentioned in this article that have an impact on your ability to positively change your body composition. Be aware of them and discuss them with your healthcare team to ensure success.

- Adequate calories and protein to support weight gain
- Exercise to ensure weight gain is muscle, not fat
- Appropriate exercise to accomplish the desired effect on body composition
- Normal testosterone levels
- Additional anabolic agents
- Dietary supplements with proven muscle enhancement effects
- BIA test to track body composition changes and adjust treatments

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Editor's Note: See the chart "Treatment for Metabolic/Wasting Disorders in HIV/AIDS" elsewhere in this issue for more information about dosing of anabolic agents.

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(continued on page 96)

EXERCISE Websites

ORGANIZATIONS

American Council on Exercise
www.acefitness.org

American Academy of Physical Medicine and Rehabilitation
www.aapmr.org

Shape Up America!
www.shapeup.org/fitness/index.htm

Positive Moves
www.positivemoves.com

EDUCATION

American College of Sports Medicine
www.acsm.org/

JOURNALS/ PUBLICATIONS

Medicine and Science in Sport and Exercise
www.acsm.org/

Yoga Journal
www.yogajournal.com

ASSESSMENT

You First Health Assessment
www.youfirst.com

YOGA FOR HIV/AIDS

For more information regarding yoga and HIV/AIDS:
www.yogagroup.org

Treatment for a Common HIV-Related Problem: Chronic Sinusitis

MISHA R COHEN, OMD, LAc

Chronic sinusitis affects over 37 million Americans every year. It is the most common chronic condition in the United States today. However, chronic sinusitis affects people with HIV/AIDS more frequently than those in the general population. It is one of the most common problems faced by people with HIV infection.

Bacteria, fungi, viruses, and environmental conditions such as molds all can cause sinusitis. The organisms that cause acute sinusitis in both immunocompromised and immunocompetent populations include *S. pneumoniae* and *H. influenzae. Staphylococcus aureus* and *P. aeruginosa* are more commonly associated with chronic sinusitis.

The American Academy of Otolaryngology—Head and Neck Surgery describes chronic sinusitis as "a prolonged sinus infection; one that usually lasts for more than three months." They go on to say: "When you breathe in through your nose, the sinuses (which are air-filled) act like a filter, which creates mucus. If your sinus pathways do not properly drain, your sinuses can become 'diseased.' This can result in difficulty breathing through your nose, facial pain, and blockage of the sinuses among other symptoms. A sinusitis condition can interfere with one's lifestyle because of the constant pain and discomfort…generally, a sinusitis condition will last more than 10 days and could also cause a discharge of thick yellow/green mucus, nasal congestion, and facial pain/pressure There is no known 'cure' for chronic sinusitis…the right treatment can help resolve a current infection, but it may reoccur."

The common complaints related to sinusitis are sinus discharge, post-nasal drip, headache, hearing problems, ear infection, a sinus cold, or sinus allergies that wax and wane. Although often the problem does not seem very acute, over time, if the condition is untreated, it can really put a burden on the immune system—especially in those who are immunocompromised—and can lead to serious infection requiring various antibiotics and other medications.

There are four main treatments a Western clinician would prescribe for chronic sinusitis infection:

Oral Antibiotics. Oral antibiotics are one of the most prescribed treatments for chronic sinusitis patients. For this treatment, doctors prescribe a number of antibiotics that a patient takes on a daily basis for usually 2 to 3 weeks.

Nebulized Antibiotics. Nebulized antibiotics treat infections topically. This method aerosolizes the drug; when you breathe it in through your nose, the drug goes directly to the source of the problem. This type of treatment usually lasts 2 to 3 weeks.

IV Antibiotics. In select cases, a doctor may decide on an intravenous (IV) antibiotic therapy. This type of therapy generally lasts 4 to 6 weeks.

Sinus Surgery. Sinus surgery is generally reserved as a last line of defense. The purpose of the surgery is to relieve the chronic sinusitis condition. The surgery is generally accomplished in 1 to 3 hours. It can take several weeks for a full recovery.

Complementary and alternative medicine (CAM) offers treatment approaches to sinusitis in both early and late stages. In early stages without severe infection, CAM practitioners often use treatment as an alternative to Western therapies. In later stages, we combine therapies with Western therapies in a complementary manner. All sinus infections and cases of sinusitis should be evaluated by a Western physician to determine whether they may be caused by opportunistic organisms so that appropriate pharmaceutical therapies can be prescribed. Chinese medicine practitioners and naturopathic doctors often use acupuncture, Chinese or Western herbs, sinus washes/steams, and massage as the basic treatment. Nutrition, including diet and nutritional supplements, is also a major part of the treatment plan.

Chinese Differential Diagnosis

Chinese differential diagnosis is important for the treatment of chronic and acute sinusitis, and your Chinese medicine doctor may make one of the following diagnoses in connection with this condition.

- Lung/spleen dampness
- Lung heat
- Lung/spleen damp heat
- Large intestine channel disturbance
- Deficient lung
- Qi stagnation

Common Chinese treatments and some variations that you might find successful are discussed below.

Acupuncture

Many sinus conditions can be managed through acupuncture and acupressure techniques that open the sinuses and help to unblock congestion in the ears.

Needle insertion points may be chosen based on the Chinese medicine differential diagnosis; other insertion points may be chosen for symptomatic relief. Local needling may be used for local discomfort on the face, neck, ear, and sinus areas. Acupuncture may be used for the following diagnoses:

- Liver–gall bladder constitutional types with heat rising
- Digestion problems
- Problems with water metabolism
- Digestion problems related to post-nasal drip
- Phlegm obstruction
- Common cold symptoms
- Sores in the nose
- Heat, infection

A practitioner may apply White Flower Oil under the nose during treatment (not too much for sensitive skin). The patient may also apply this product at home. Any Chinese herb store and many natural products stores carry White Flower Oil.

Acute or difficult situations may require acupuncture treatments at least twice a week.

Nasal Wash

A nasal douche can be performed using a glass irrigating bulb. We recommend the following technique:

- Use a mild salt-water solution in a glass nasal douche to gently clean sinus passages. Use sea salt or kosher salt. DO NOT use commercial table salt, which contains chemicals that keep the salt from forming clumps in the shaker! Use only spring water that is not chlorinated, filtered water, or boiled (i.e., dechlorinated) tap water. One can also let water sit in a clear glass bottle in the sunshine with a loosely fitted lid for a day; this will also break down and clear the chlorine. Warm water feels much more comforting than cold. Too warm may be painful. Begin with a proportion of 1/2 to 1 tsp. of salt to 1 cup of water. Work up to 2 tsp. of salt per cup of water.
- You may also perform a nasal douche using warm water alone.
- Using a glass nasal douche (available at some pharmacies and clinics), gently pour several drops of the water solution into each nostril, tilt the head back, and hold the opposite nostril closed. Let the solution run into the sinuses or down the throat. Repeat 3–5 times on each side. Be careful not to force the solution into the sinuses with too much pressure. If the ears are congested, be very gentle and use small amounts of water to begin with.

In this procedure, you may feel a sharp sensation, lasting only a few seconds, in the areas

with damaged tissue. In the course of the therapy, this discomfort will subside as the tissues heal. The benefits are worth the temporary discomfort. After a few treatments, the sinuses will begin to drain, and as old build-ups begin to work loose, phlegm of various colors and consistencies will be discharged. These discharges are a normal part of the treatment and should not alarm you.

Herbs

Many herbal remedies are used by Chinese practitioners in treating chronic sinus conditions.

Chinese Patent or Pill Formulas. Some Chinese herbal formulas for sinus congestion can be purchased over the counter. I recommend using GMP (Good Manufacturing Practices) –labeled formulas for safety reasons and to be sure there are no harmful pharmaceuticals or toxins in the herb pills. For example, in our clinics we use Pe Min Kan Wan (Plum Flower Brand; May Way Herb Company) with green or black tea.

Cooked Bulk Herb Formulas. A qualified trained Chinese or Western herbal practitioner may prescribe cooked herbs, which are excellent for sinusitis and allergic symptoms. The herbal decoction may be taken hot or warm; before drinking it one should inhale the steam, thus steaming the sinuses with the herbs before drinking them. You can also place essential oils below the nose in order to inhale their scent. However, follow your practitioner's instructions for specific formulas and treatments.

A typical Chinese herb formula to Relieve Dampness, Stop Cough, and Open Sinuses includes the herbs Xing Ren, Jie Geng, Zi Wan, Chen Pi, Lu Gen, Ma Huang, Gan Cao, Xin Yi Hua, Cang Er Zi, and Bai Ji Li. (One should only use the formula that your practitioner has prescribed.)

Formula variations are made according to the differential diagnoses and symptoms.

- With heat, add: Ban Lan Gen, Da Qing Ye, Ju Hua, Huang Qin, Jin Yin Hua
- With pain, add: Bai Zhi
- With spleen damp, add: Fu Ling
- With dryness, add: Tian Hua Fen
- With headache, add: Chuan Xiong
- With Qi stagnation, add: Chai Hu, Xiang Fu

Steaming Herbs. Throughout the day vaporize eucalyptus, rosemary and/or thyme in fresh herb form or as essential oils. Thyme is considered the strongest antibacterial antisinusitis herb. Red thyme is considered to have the strongest effect.

Add herbal essential oils to hot water (in a portable mug or in a simmering kettle), to a vaporizer, to an essential oil atomizer, to a candlestick oil evaporator, or simply to a sink and cover the head with a towel tent. Close your eyes, and breathe in the vapor.

In addition to the above herbal remedies, horseradish is a great condiment for treating sinusitis. (Of course, one should only inhale the aroma or place a small amount on the tongue; one should never place the herb directly in the nasal cavity.) To manage sinusitis long-term, continue treatment with Pe Min Kan Wan as explained above.

Massage

You can perform acupressure on the sensitive spots on the forehead, hairline, cheeks, nose, ears, and palate. The acupuncture points mentioned earlier may also be used for sinus massage. Reflexology massage on the associated fingers and toes can be very helpful. For blocked ears, massage behind the ears with White Flower Oil a couple of times a day.

Conclusion

The above treatments and home remedies, if done consistently for 2 to 3 months, can have profound healing effects on chronic sinus infections, allergies, asthma, chronic coughs, or post-nasal drip. For mild low-grade sinus conditions, CAM therapies may often be used alone. For more serious infections, a Western practitioner should be consulted to determine the cause and prescribe appropriate therapies.

A treatment plan combining both CAM and Western conventional therapies is the best approach for people who are immunocompromised.

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Some useful websites:
www.chronicsinusitis.com
www.chronicsinusitis.com/treatments.html

COMPLEMENTARY Websites

GOVERNMENT

National Center for Complementary and Alternative Medicine
http://nccam.nih.gov

ORGANIZATIONS

Acupuncture
www.acupuncture.com

AIDS, Medicine and Miracles
www.csd.net/~amm

American Academy of Medical Acupuncture
www.medicalacupuncture.org

American Association of Naturopathic Physicians
www.naturopathic.org/

American Association of Oriental Medicine
www.aaom.org

American Chiropractic Association
www.amerchiro.org

American Holistic Health Association
www.ahha.org

American Holistic Nurse's Association
http://ahna.org

AIDS National Interfaith Network
www.thebody.com/anin/aninpage.html

Alternative Medicine Foundation
www.amfoundation.org

American Society of Pharmacognosy
www.phcog.org

Herb Research Foundation
www.herbs.org

Doc Misha's Chicken Soup Chinese Medicine
www.docmisha.com

HerbMed
www.herbmed.org

The Alternative Medicine Homepage
www.pitt.edu/~cbw/altm.html

Tibetan Medicine
www.tibetmedicine.org

EDUCATION

Bastyr University
www.bastyr.edu

Department of Pharmacognosy University of Mississippi
www.olemiss.edu/depts/pharmacognosy/

Rocky Mountain Herbal Institute
www.rmhiherbal.org

JOURNALS/PUBLICATIONS

Alternative Medicine Review
www.thorne.com/altmedrev/index.html

Journal of Natural Products
http://pubs.acs.org./journals/jnprdf/index.html

The Expanded Dictionary of Metaphysical Healthcare
http://hcrc.org/diction/dict.html

DATABASES

Health World
www.healthworld.com

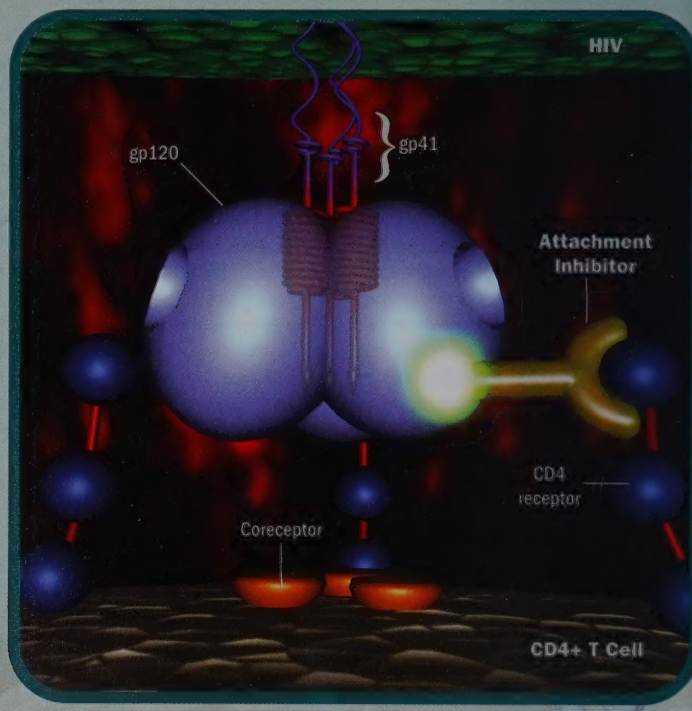
Health WWWeb
www.healthwwweb.com

HerbNet Information Center
www.herbnet.com

Herbal Information Center
www.healthy.net/clinic/therapy/herbal/herbic/index.html

Entry Inhibition:
New Targets for HIV Therapy

Antiretroviral therapies such as Reverse Transcriptase Inhibitors and Protease Inhibitors prevent viral genome replication and viral maturation intracellularly, after HIV has infected the CD4 cell. HIV entry inhibitors target the virus before it enters the CD4 cell. By blocking viral infection, entry inhibitors stop viral replication. Entry inhibitors currently in development target three different points in the entry process: (1) attachment to CD4 cells, (2) coreceptor binding and (3) viral fusion.



Attachment Inhibition

The first step in the process of viral entry involves the interaction between HIV's external viral envelope glycoprotein, gp120, and domains on the CD4 receptors that allow binding and attachment to occur. Investigational attachment inhibitors target this initial stage of CD4 receptor binding to viral gp120 and disrupt the process that brings viral gp120 into close proximity with the coreceptors.

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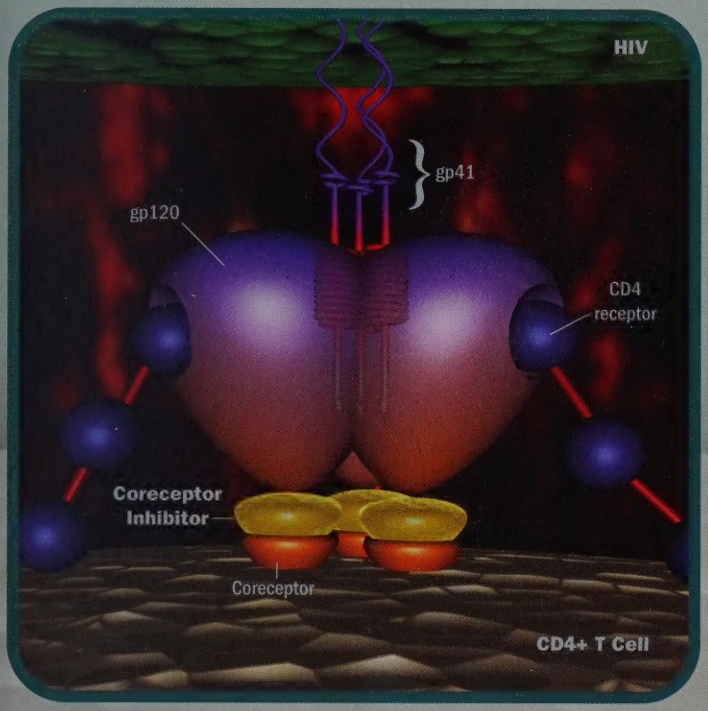
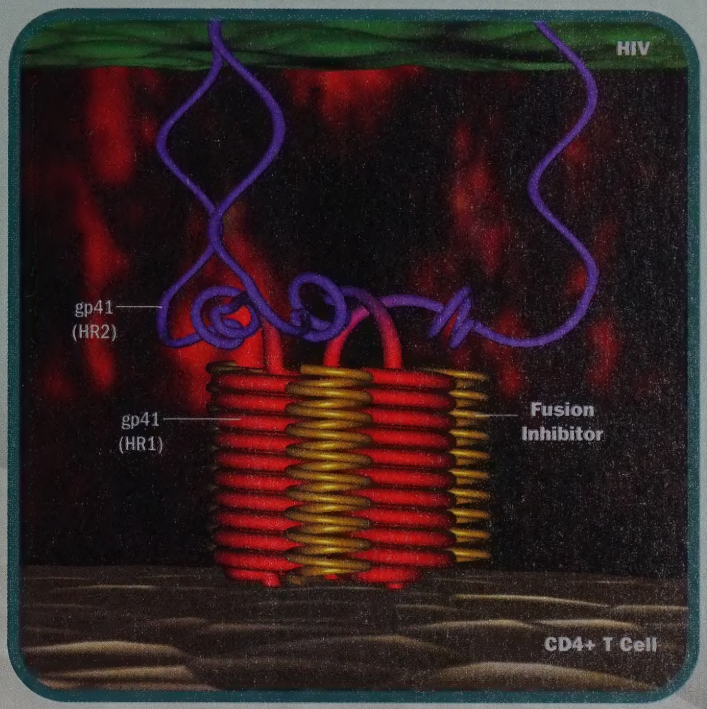
Targeting HIV *Outside* the Cell[1,2]





Coreceptor Binding Inhibition

Following the interaction of gp120 with the CD4 receptors, a structural change is believed to occur within gp120 that allows further interaction between gp120 and the major HIV coreceptors, CCR5 and CXCR4. CCR5 and CXCR4 inhibitors in development target the process of gp120 binding to these coreceptors.

Fusion Inhibition

Conformational changes occur in gp41 following the interaction between gp120 and the CD4 receptors and coreceptors. These changes allow gp41 to anchor to the host cell membrane and drive fusion of the viral membrane with the cell membrane. Membrane fusion creates a fusion pore large enough to allow the HIV capsid to pass into the CD4 cell. Synthetic peptide fusion inhibitors block key structural changes in gp41 that facilitate membrane fusion, thereby preventing the injection of the viral genome into the healthy CD4 cell. Peptide fusion inhibitors are in late stage clinical development.

Partnering to Expand Treatment Options

Hoffmann-La Roche Inc. (Roche), a leading research and manufacturing based healthcare enterprise, and Trimeris, Inc., a biopharmaceutical company, are committed to the discovery of antiretroviral agents aimed at new viral targets, mobilizing the resources necessary to advance the development of breakthrough treatments for people living with HIV/AIDS. Roche has demonstrated a long-term commitment to HIV/AIDS and ranks among the world's leaders in pharmaceuticals and diagnostics. Trimeris is engaged in the discovery and development of novel therapeutic agents to treat viral diseases. The core technology platform of fusion inhibition is based on blocking viral entry into host cells. Through an innovative partnership, Roche and Trimeris have achieved a leadership position in the research and development of fusion inhibitors.

Roche Pharmaceuticals

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www.trimeris.com

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The Global Business Coalition on HIV/AIDS (GBC) States That Managing HIV in the Workplace Must Be Standard Business Practice: New Web-Based Road Map Shows How

BEN PLUMLEY, EXECUTIVE DIRECTOR, GLOBAL BUSINESS COALITION ON HIV/AIDS

On World AIDS Day 2003, the Global Business Coalition on HIV/AIDS (GBC) launched the latest phase of its campaign to increase dramatically the number of HIV workplace programs implemented by employers around the world. "Managing HIV in the Workplace" is a web-based guide to over fifty company HIV programs, representing different industries, workforce sizes, and geographical locations. Common to all programs, however, is the need to prioritize nondiscrimination, prevention, testing, and treatment programs.

Richard Holbrooke, President and Chief Executive Officer of the GBC, has said, "The greatest immediate responsibility—and opportunity—for individual companies is to protect their employees and immediate families against the spread of the epidemic. In many countries, workplace programs will be the only accurate source of information employees will have about HIV/AIDS. The business sector has the unparalleled opportunity to tackle head on the stigma and discrimination that have enabled this virus to spread, often unchecked, over the last twenty years."

"Managing HIV in the Workplace" can be found online at the newly redesigned GBC website at: www.businessfightsaids.org. It is targeted to business managers who are establishing their own programs and who are looking to learn from the experience of other employers. Many of the companies participating in this initiative have provided extensive and previously unavailable data. In addition, the GBC has included employee programs from international agencies and nongovernmental organizations.

According to Solly Molekwa, Regional Employee Wellness Manager of British Petroleum (BP), "Managing HIV in the workplace represents information-sharing and collaboration not just within the business sector, but incorporates international agencies, nongovernmental and community-based organizations, and private healthcare providers. Pooling information on this level enhances greater business action and creates a platform for innovative approaches and new partnerships."

Speaking in New York at a World AIDS Day event organized by the American Foundation for AIDS Research (amfAR) and Columbia University, Ben Plumley, Executive Director of the GBC, said, "We now have [a] baseline of the best company programs from around the world, from which we can identify the obstacles to reaching the greatest number of employees—and [identify] how business creativity can be applied to overcome them."

Through review of anecdotal evidence and trends, the following key challenges have emerged:

- A number of companies report that the take-up by staff of services is low, despite the establishment and promotion of comprehensive workplace programs. There appears to be a range of reasons for this, particularly the fear of disclosure of HIV status in the workplace and its potential impact on job security.
- Therefore, strong senior-management endorsement of company nondiscriminatory policies (on the basis of perceived and actual risk of HIV infection) is critical to encouraging staff to seek voluntary counseling and testing, and to access prevention and treatment services.
- By focusing on the urgent need to implement programs, less attention has been paid in many companies to monitoring the effectiveness of their programs.
- Private-sector employers in regions heavily affected by HIV/AIDS continue to need access to the low-cost diagnostics and medications to treat HIV/AIDS that have been made available to the public sector by a range of manufacturers.

GBC's campaign to make HIV workplace programs standard business practice is supported by a working group of companies and relevant experts, and by other groups like WEF's Global Health Initiative, who helped develop a number of company submissions. In 2003, the campaign will continue with a number of expert meetings that will address the obstacles and challenges faced by the business sector in implementing workplace interventions. The meetings will bring together company managers, public health specialists, pertinent service organizations, and financing representatives. The first meeting on ARV access through the workplace is being planned with the help of PharmAccess International and STOPAIDSNOW! for the end of March. Other meetings will focus on testing, prevention and education, and monitoring and evaluation.

The GBC's membership currently stands at 104 companies (a list of all GBC member companies can be found online at: www.businessfightsaids.org). This rapidly expanding alliance of companies is dedicated to combating the AIDS epidemic through the business sector's unique skills and expertise. The GBC is led by Chairman Juergen Schrempp (Chairman of DaimlerChrysler), President and CEO Richard Holbrooke, and Executive Director Ben Plumley, who is on secondment from UNAIDS.

The GBC mission is to increase significantly the number of companies committed to tackling AIDS, and to make business a valued partner in the global efforts against the epidemic. HIV/AIDS should be a *core business issue* for every company, particularly those with interests in heavily affected countries. With the support of global leaders in government, business, and civil society, the GBC promotes the broad range of valuable contributions that business can make, through policy development and by identifying examples of good practice.

In advocating for greater business action on AIDS, the GBC believes that business can respond in three main ways:

- **By implementing prevention and care programs and policies** for employees and immediate communities. In many countries, company programs will be the only source of accurate HIV information available to employees.
- **By using the core business strengths of creativity and flexibility** to improve the reach and effectiveness of AIDS programs. The marketing, communication, distribution, and logistics skills of business are already strengthening the impact of many AIDS programs around the world.
- **By business leadership and advocacy** that lobbies for greater action and partnerships with governments and civil society.

Ben Plumley is working to transform the business response to the epidemic. Ben's involvement in HIV/AIDS extends back to 1989 and spans the public and private sectors. Most notably, Ben has worked in a range of AIDS service organizations; he spent five years as an executive in the pharmaceutical industry and has served as a Policy Advisor at UNAIDS. Ben is currently on secondment from UNAIDS.

For more information on The Global Business Coalition on HIV/AIDS, please visit: www.businessfightsaids.org N

GLOBAL BUSINESS COALITION ON
HIV/AIDS

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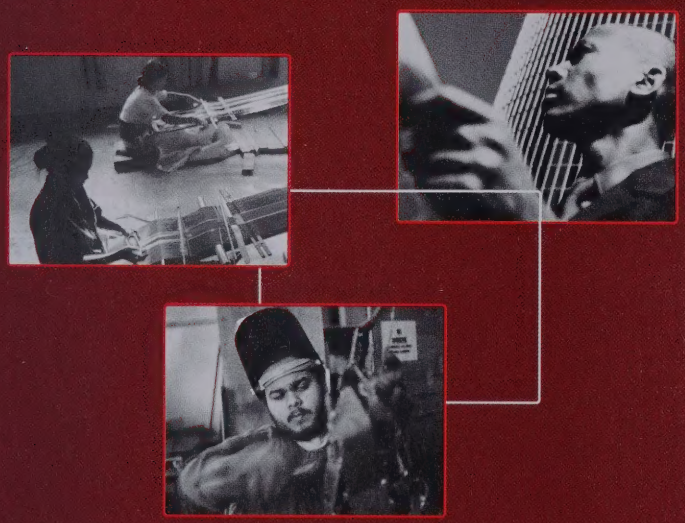

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The International AIDS Trust Checks In

SANDY THURMAN, FOUNDER AND PRESIDENT, INTERNATIONAL AIDS TRUST (WITH BENJAMIN RYAN)

We are losing the global war on AIDS. Twenty-two years of hard-fought efforts have yielded insufficient progress, and we are faced with sobering statistics. To date, AIDS has killed 25 million men, women, and children worldwide. With each passing day, 8,000 more people die, and 14,000 others join the ranks of the 40 million living with HIV/AIDS. If current trends continue, 100 million will be infected by the decade's end. At that time, there will be more than 44 million orphans—as many as the number of students in American public schools. And while a devastated Africa holds the current epicenter of the disease, troubling reports predict more than 10 million cases of HIV in China by 2010; India's cases may already outnumber South Africa's.

Beneath these cold figures is the even colder truth of a disease that denigrates the very social fabric of our world's many great nations. AIDS undermines basic education because children drop out of school to care for dying parents or to support younger siblings left behind. National economies suffer in tandem with the sick: AIDS strikes down workers in their prime, drives up the cost of doing business, and slashes the gross domestic product. The growing pandemic threatens international security by undermining conflict resolution and reconstruction, complicating peacekeeping efforts, and destabilizing militaries.

We must accept that we have failed to stop this devastation, and use that regret as galvanizing motivation to change the seemingly unchangeable. Because, as grave as the status quo may be, opportunity for successful progress is within our reach. According to a recent Bill and Melinda Gates Foundation report, we can save 30 million lives by 2010 just by applying the tools we already have at our disposal. To do so, we need to change the fact that, given the magnitude of the crisis, the current scale of efforts is too small, resources are too few, and leadership is too scarce.

That's where the International AIDS Trust (IAT) comes in. Since our founding in August 2001, we have sought to mobilize the public and the political will, funding, and action needed to effectively fight AIDS worldwide.

Thanks to the tireless efforts of an international team that includes former Presidents Bill Clinton and Nelson Mandela, we are beginning to turn the wheels of progress toward fusing international policy, politics, and public relations in a synergized global war against humankind's greatest plague.

A top priority of IAT is to realize the dream of UN Secretary General Kofi Annan, who has called for $10 billion annually to fight global AIDS. We feel that the fight against AIDS, to which the US government has committed about $100 billion since 1981, deserves no less. IAT and UNAIDS have joined forces to create America's World Action Campaign to Stop AIDS. Together, we will work to mobilize the United States—both in the public and private sector—to contribute its fair share to the war on AIDS. That means a full $2.5 billion a year, not the current public/private combined total of about $1 billion. We will formally launch the campaign at a televised concert at Radio City Music Hall on May 5, 2003, hosted by IAT Advisory Board member Whoopi Goldberg, who once masterminded the highly successful Comic Relief concerts.

In addition to this domestic effort, IAT and UNAIDS are seeking to prompt increased funding contributions abroad by enlisting the help of NGOs in major donor nations and in countries with serious or newly emerging epidemics. These civil society leaders will form a global federation, to be co-chaired by IAT and UNAIDS, that will share expertise and experience and move toward a coordinated global response to the epidemic.

IAT is committed to moving HIV treatment into countries where such a promise remains a distant reality. To push past polarization around intellectual property issues and toward providing proper HIV care, we developed the "family package" demonstration program for the First Lady of Rwanda. By providing affordable treatment to HIV+ parents and their children, this pilot program will seek to prove that the most effective way to increase access to care is to expand existing efforts to prevent mother-to-child transmission of the disease.

The terrorist attacks of September 11 and the subsequent war on terrorism have pushed global AIDS down the list of top global priorities. IAT has entered into the global dialogue the fact that AIDS plays an integral part in international security concerns. We joined with the International Crisis Group in the creation of a widely read analysis of how AIDS threatens security, providing recommendations on actions for donor nations, the UN, affected countries, and the private sector. The report not only formed the basis of a briefing on Capitol Hill, but was also used for hearing and debate in the European Union and in several European Parliaments.

Thanks to generous funding from the Bill and Melinda Gates Foundation, we have begun to translate pledges and promises into real results with the Organization of African First Ladies Against AIDS. As the most visible mothers of Africa, these women will focus much needed attention on the special challenges facing those affected by HIV/AIDS. IAT has already helped to structure the organization and to develop its strategic plan, and is working with other groups to secure funding for communications and advocacy training as well as programmatic activities at national and regional levels.

The First Lady of Ghana has said that "In the history of the world and of mankind, it has always taken men and women of courage to lead and others to follow." IAT and UNAIDS worked to foster such courage with the first-ever "leadership institute" at the Barcelona International AIDS Conference in July 2002 by bringing world leaders and decision makers into the conference deliberations. IAT and its many partners look to the future with hope as we continue to plan how to fight this disease multilaterally. We are currently working with UNAIDS to recruit international leaders—including past and present heads of state, parliamentarians, and religious leaders—to form a broad-based network to cultivate and support leadership. Because it is with courageous unity that we can turn the tide on the tragedy of our time, as it continues to swell and threatens to engulf us.

For more information please visit us online at: www.internationalaidstrust.org.

Sandy Thurman is a former AIDS policy advisor to President Clinton. Ms. Thurman is the founder and president of the International AIDS Trust. N

EVERY DAY 8000 PEOPLE
DIE OF AIDS

INTERNATIONAL AIDS TRUST

The International AIDS Trust (IAT) is a single-focused NGO with the access and vision needed to effectively fight AIDS worldwide. Based in Washington, D.C., IAT works at home and abroad to advocate sound policy, create strategic partnerships, and increase awareness of the global AIDS crisis and the opportunity to make a difference. IAT reaches out to heads of government, policy makers and parliamentarians; labor, business, faith and foundation

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Doctors of the World: A Call for Advocacy

TOM DOUGHERTY, MPH, ACTING EXECUTIVE DIRECTOR, DOCTORS OF THE WORLD—USA

Injection drug users are often the forgotten face of HIV internationally. Sadly, at the International AIDS Conference in Barcelona in July 2002, as at other AIDS conferences, there were few people advocating for the rights of injection drug users (IDUs), despite the fact that 22 years into the pandemic there are an estimated 3 million past and current IDUs living with HIV worldwide.[1] IDUs remain a key vulnerable population in the transmission of HIV and are frequently discriminated against (even within HIV advocacy communities). It is still considered appropriate to "blame" injection drug users for their HIV status. "They asked for it, they deserved it, they did something wrong, and this is their punishment" are among the phrases that remain in the lexicon used to describe IDUs living with HIV and AIDS.

In addition to being vulnerable to HIV, hepatitis, and other infections, IDUs face further stigma when they seek the medical care and assistance they require. Many healthcare professionals and other providers of essential services remain reluctant to treat active drug users, and barriers are often erected to discourage their participation and access to care. It is time for the world of HIV advocacy, prevention, care, and support service providers to move beyond a language of blame and to aggressively address the rights and needs of IDUs living with HIV around the world.

While injection drug use and the treatment of IDUs with HIV are problems around the world, a prime example of the effectiveness of intravenous drug use as a means of spreading HIV can be found in the former Soviet Union. Previously characterized by very low HIV prevalence rates, the region now faces an extremely steep increase in the rate of new infections.[2–4] In the Russian Federation alone, new cases of HIV have increased from 420,000 at the end of 1999 to over one million in 2001. Throughout the former Soviet Union, between 50 to 90 percent of new HIV infections since 1995 are among IDUs. By comparison, as of 2001, only 14 percent of the cumulative HIV cases in the United States resulted from injection drug use alone.[5]

Beyond providing a dramatic example of intravenous drug use's effectiveness as a means of increasing infection rates, the situation of IDUs with HIV in the former Soviet Union also illustrates the degree to which IDUs with HIV are significantly marginalized, are often criminalized, and regularly suffer from limited access to treatment. Throughout the former Soviet Union, the most common interaction of IDUs with the government occurs via the criminal justice system, where those with HIV have little hope of receiving any treatment. Those IDUs who do have access to medical services receive them from clinicians who too often have little desire or capacity to treat them effectively.

Currently, only limited treatment of opportunistic infections (OIs) is available in Russia, and there is virtually no access to antiretroviral therapy. Treatment for tuberculosis (TB), the most common OI, occurs only through TB hospitals. Prophylactic treatment of latent TB is not used in the care of HIV patients, and there is a common misperception that people living with HIV are less likely to respond to TB treatment because of their immune status. Use of TMP/SMX chemoprophylaxis, a recommended practice in the United States for the prevention of *pneumocystis carinii pneumonia* (PCP) AIDS patients, remains unavailable in the former Soviet Union. There is an urgent need to develop more projects with adequate structures for monitoring and evaluating prophylactic treatment for OIs and treatment of IDUs in resource-poor settings like the countries of the former Soviet Union.[6]

As a part of Doctors of the World's (DOW) commitment to health and human rights, we are working with Russian harm-reduction sites and government-supported AIDS centers to develop and enhance HIV prevention, care, and support strategies for IDUs in the former Soviet Union. DOW has established local partnerships to initiate four pilot programs in Kazakhstan, Russia, and Ukraine where testing, counseling, clinical care, and support services will be offered in concert with harm-reduction efforts to facilitate secondary prevention, care, and support for people living with HIV, especially IDUs. The initiative
will build upon targeted government-supported testing programs and civil society-supported efforts at primary prevention to further support the efforts of both in addressing HIV prevention and care. The goal is to reduce the number of new infections annually to lessen the medical and psychosocial impact in the former Soviet Union and the world.

Doctors of the World is a US-based nonprofit 501(c)(3) international health and human rights organization. Founded in 1990 by a group of physicians, including the late Dr Jonathan Mann, Doctors of the World mobilizes the health sector to promote and protect basic human rights and civil liberties for all people, in the United States and abroad.

Tom Dougherty, MPH, is currently the acting Executive Director of Doctors of the World—USA. Prior to his work in international health, he developed and administered HIV treatment centers focused on access to care for drug users in New York City. N

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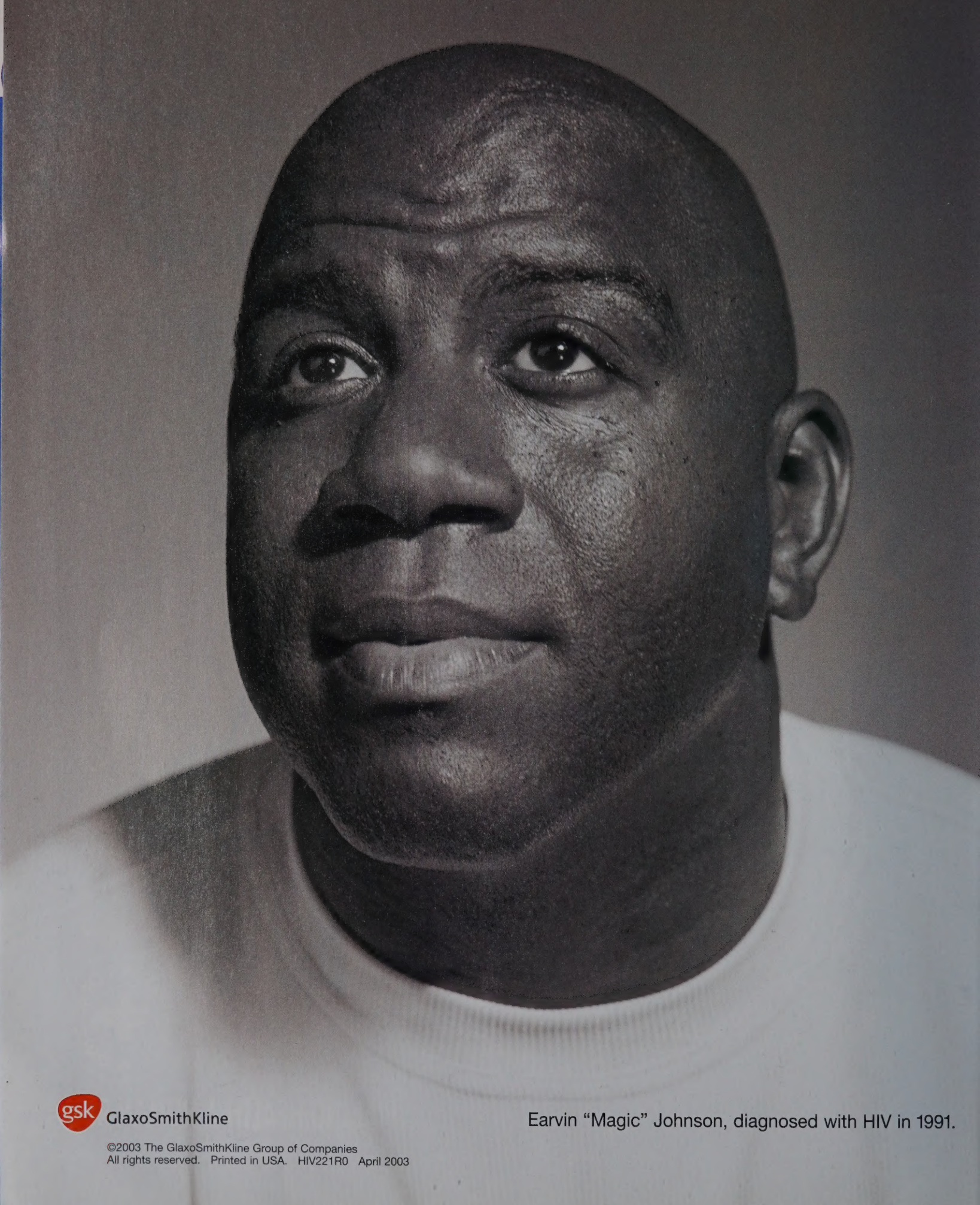

GlaxoSmithKline

Earvin "Magic" Johnson, diagnosed with HIV in 1991.

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A positive attitude

Partnering with my doctor

Taking my medicine every day

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For information about living with HIV, call 1-888-TREAT HIV or visit www.TreatHIV.com.

ADAP IN PERIL

ELIZABETH HEUBECK

NUMEDX

Since 1987, the AIDS Drug Assistance Program (ADAP) has been used to bridge the gap in funding HIV/AIDS prescription drugs for the uninsured and underinsured. Like many bridges, ADAP wasn't prepared for the increasingly excessive use it has been forced to endure. And like many heavily used bridges, funding to maintain its strength varies greatly among districts, so that in some areas it remains sturdy—a virtual gateway to a host of treatment options—whereas in other sections, the bridge has begun to buckle, collapse appearing imminent.

ADAP's pending crisis provokes several questions. Why is ADAP's "pavement" so uneven across states? Will its entire infrastructure survive the toll of increasingly heavy traffic? Can viable solutions, such as the creation of new traffic patterns, ease the overwhelming weight that ADAP shoulders? Before attempting to arrive at solutions to ADAP's current challenges, it will help to understand why and how the program was originally established.

In late 1995, expensive combination antiretroviral therapy costing between $10,000 and $12,000 a year was introduced as the standard of care. As the treatment paradigm for people living with HIV/AIDS changed dramatically, so did the demands placed on ADAPs.

History of ADAP

Fifteen years ago, Congress approved an emergency appropriation of $30 million for states to provide AZT, the first and then only FDA-approved antiretroviral drug, to people with HIV/AIDS. Since then, the formerly named AZT Assistance Program, as well as the HIV/AIDS epidemic, has become far more complex than anyone could have originally anticipated.

In the early years, people took AZT as primarily a palliative measure; no one who had the disease expected to survive very long. This was still the case in 1990 when the AZT Assistance Programs, and other approved antiretroviral medications and drugs to prevent and treat opportunistic infections, were absorbed into Title II of the Ryan White Comprehensive AIDS Resources Emergency (CARE) Act. In keeping with its expanding nature, the program's name was then changed to the AIDS Drug Assistance Program, or ADAP. In late 1995, expensive combination antiretroviral therapy costing between $10,000 and $12,000 a year[1] was introduced as the standard of care. As the treatment paradigm for people living with HIV/AIDS changed dramatically, so too did the demands placed on ADAPs.

Because combination therapy brought with it the hope of longer and healthier lives, more people than ever before sought testing and treatment. In the latter half of 1996 alone, ADAP enrollment increased 23 percent overall. In some ADAPs, enrollment soared 50 percent or more. In response, Congress appropriated supplemental funding for ADAPs, which resulted in a 97 percent increase of $182 million in the national ADAP budget between FY 1996 and FY 1997.[2]

In FY 2001, the national ADAP budget reached $810 million, representing a 329 percent budget increase since 1996.[2] Behind Medicare and Medicaid, the Ryan White CARE Act—most of whose dollars go to ADAP—is the third largest source of federal funding for HIV/AIDS care. That seems like a lot of resources allocated to the treatment of HIV/AIDS for those who lack sufficient insurance. But when you consider the stark facts about how many individuals have HIV/AIDS, the percentage of those folks who lack insurance, and what it takes to treat the disease, the woefully inadequate amount of funding for ADAP becomes clear.

Gaping Funding Inadequacies

Here are the numbers. Approximately 900,000 people in the US are living with HIV/AIDS.[3] One of every five of those individuals is uninsured. Annual costs to treat HIV/AIDS rise to approximately $20,000 per patient when you add to combination therapy the expenses of doctor visits, laboratory tests, and drugs to prevent or treat opportunistic infections.[4] Treating these 180,000 or so uninsured people who have HIV/AIDS in the US would cost over $3.6 billion annually. And yet total federal spending on HIV/AIDS Care for FY 2000 was $6,172 million.[5] Needless to say, that amounts to an enormous shortfall.

In addition to this current gaping shortfall of federal dollars for HIV/AIDS treatment, the picture for FY 2003 looks no less bleak. In announcing his budget proposal for FY 2003, President Bush indicated that funding levels for the Ryan White CARE Act would remain the same as last year, at $1.9 billion. Approximately $639 million of this funding is allocated for ADAPs.[6]

Any increases in HIV/AIDS funding for FY 2003 were squelched due to a "major increase" in federal dollars to prevent bioterrorism— a threat of unknown proportions. Meanwhile, the very real and present HIV/AIDS epidemic has already claimed the lives of 438,795 Americans.[3]

Dramatic Differences Among State ADAPs

Since the inception of ADAP, funds for the program have come primarily from federal dollars, although some support does come

from individual states. In FY 2001, 38 states provided state general revenue support to ADAPs.[2] Each state, however, administers its own ADAP program, establishing financial and clinical eligibility criteria as well as drug formularies.

As a result, wide variability exists among state ADAPs. To a large extent, these inconsistencies can be attributed to the total amount of resources that a state budgets for HIV/AIDS treatment, such as Medicaid programs and indigent/uninsured care programs. The stronger the overall infrastructure, the smaller the gap that ADAP must fill.

Differences among state ADAPs cut across every aspect of the program. For instance, financial eligibility ranges from a low of 125 percent of the Federal Poverty Level (FPL) in North Carolina, or just over $10,000 a year, to a high of 500 percent or more in Massachusetts, New Jersey, and New York. Clinical criteria vary, too. In some states, patients must have a specific CD4 count or viral load range before they can access ADAP; in others, proof of an HIV-positive test is sufficient. The number of drugs included in ADAP formularies also differs dramatically from one state to the next. Louisiana and Utah, for instance, cover only 18 drugs, whereas New York covers 471. Coverage of drugs to prevent and treat opportunistic infections also runs the gamut. A few states don't cover any of these drugs, but 36 states do cover at least 10 or more of them.[2] A recent report noted that ten states currently have program restrictions, while several other states are preparing to implement restrictions in the near future.[7]

Numbers tell part of the story. But when examining the health of a program as broadly used as ADAP is—in June of 2001, the number of patients served by ADAP reached 76,743[2]—it is essential to look beyond these "objective measures" as compiled by statisticians and to hear what those in the trenches have to say. By all accounts, their stories vary as widely as the numbers do.

Texas in Turmoil

Of the nation's 50 states, Texas ranks fourth in the number of HIV/AIDS cases reported. Despite Texas's large HIV/AIDS population, Dr. Caroline Parker, executive director of the Texas AIDS Network, describes the state's ADAP as "comparatively weak."

The Texas ADAP suffers from limited eligibility, a sub-par drug formulary, and the threat of eliminating access to prescription drugs for those currently benefiting from them. "It never included all the medications for treatment of HIV and related conditions. As for drugs for side effects from HAART—don't even think about it," Parker says. To be eligible for the program, a person must be at 200 percent of the federal poverty guidelines, although the guidelines are eased somewhat by "backing out" the cost of HIV/AIDS medications. And due to projected shortfalls of $13 million in 2004 and $17 million in 2005, Texas may be forced to apply program restrictions that would place further limitations on eligibility enrollments. As a result, 2,500 of the 11,092 clients currently enrolled and receiving life-saving medications through ADAP would be dropped from the program. An estimated 1,700 potential new enrollees over the next 32 months would be turned away.

When asked whether Texas's other state-funded programs may be able to shoulder some of the burden that the Texas ADAP seems unable to endure much longer, Parker pauses, as if searching for an answer, before responding: "I've been looking, I promise you. By the time you get to the fact that you're not a pregnant woman, or at 25 to 30 percent of the federal poverty level, or aged, there's little hope." Then she adds: "We do provide medications for prisoners. So if you rob a bank, you're guaranteed medication."

There are prospects of additional assistance, from outside and from within ADAP, but Parker doesn't sound optimistic about how far they'll go to pull Texans with HIV/AIDS out of their current predicament. Parker mentions the possibility of patient-assistance programs through pharmaceutical companies, but voices concern about a private safety net for a public health problem. Texas might also find relief in the form of a supplemental grant funded through Title II of the Ryan White Reauthorization Act, in which states with funding shortfalls can reserve 3 percent of their overall ADAP allocation for discretionary supplemental ADAP grants. But it may be the case of too little, too late. Also, the fund requires states to contribute $1 for each $4 in federal funds.

Although she is quick to point out the system's inadequacies, Parker maintains hope. "The people in Texas have really wonderful bedrock values. Some might say they're conservative, but they're also compassionate—they care. So as we get more people aware of the issues, and talking to legislators, we might see change," she says.

In the meantime, Parker plods on, hoping to find relief for the people of Texas with HIV/AIDS wherever she can. "I know we have a so-called budget shortfall in this state, and there aren't enough dollars to go around. But the reality of HIV is that you pay for it. I say let's pay for it up front. Let's take care of this problem before it becomes a hospital problem, where it is much more expensive," she says.

New York's ADAP: a Beacon amid Darkness

Whereas the weakness of the Texas ADAP reflects shortcomings in the state's entire infrastructure for providing healthcare assistance to residents in need, the strength of other ADAPs is indicative of state governments that support strong and easily accessible healthcare systems for the underinsured and uninsured, including people with HIV/AIDS. Such is the case in New York.

New York's ADAP has historically offered services above and beyond prescription drugs. In addition to its broad formulary of prescription drugs, the state's ADAP offers ADAP-Plus, an array of ambulatory services delivered by over 4,000 healthcare providers who offer quality care in a culturally sensitive and supportive environment. Ninety-five percent of all New York ADAP enrollees choose to take advantage of ADAP-Plus. Far fewer (8%) participate in the state's HIV Home Care program, which is also part of the state's ADAP. Thanks to the success they've achieved through highly active antiretroviral therapy (HAART), most participants don't require home care. A fourth program component is ADAP

Plus Insurance Continuation, which pays the health insurance premiums of people living with HIV/AIDS who have lost employment and are able to continue their health coverage (COBRA), as well as others for whom the cost of premiums is a financial burden.

Strong support from the state government, a comprehensive Medicaid program, and creative partnerships between state and city organizations coalesce to make New York's ADAP strong and effective. New York's Governor George Pataki has worked to provide more prevention and treatment services for people with HIV/AIDS than any other state in the nation. The state's expansive Medicaid program, including a complete range of medical services and drugs to low-income residents, does not require that a person be disabled before enrolling, thereby narrowing the "gap" that ADAP is asked to fill. Collaborative planning and funding efforts between the state health department's AIDS Institute and the New York City HIV Planning Council resulted in the establishment of ADAP-Plus. The leadership of these two organizations galvanized additional support; as a result, the remaining Title I HIV Planning Councils have joined in the partnership.

Foreboding Cuts across States

Although most funding for ADAPs comes from the federal government, support from individual states clearly makes a difference in the programs' effectiveness. But even in states that make HIV/AIDS treatment a priority, the threat of pending struggles looms large. Consider the scenario in California.

According to Anne Donnelly, director of public policy for the national HIV/AIDS advocacy organization Project Inform, "California, both the legislature and the administration, has been very, very supportive of ADAP. Up until now, we have not had a tremendous struggle…the state government just put $22 million into ADAP and a diagnostic reimbursement program. But at the federal level, we have no additional new funds. The adequacy of the federal funding is diminishing. I don't know how long the state can fill in that gap. The state has a big commitment to this, but it also has a $26 million deficit."

Even New York's "model" ADAP is feeling the pinch. In an FY 2002 report distributed by Jules Levin of the National AIDS Treatment Advocacy Project, Levin wrote "…a number of jurisdictions with currently fiscally stable ADAPs (e.g., Florida and New York) report the potential need to implement ADAP restrictions based on current funding levels and projected trends in program utilization."[8] Sooner than expected, Levin's foreboding words have become a reality.

In January 2003, New York's ADAP was forced to enact some restrictions that would allow the program to continue new enrollments and maintain core services. These changes include the following: mandatory generics when A-rated generic equivalents for a brand-name drug exist; a limit on prescription refills and nutritional supplements; a cap on clinic and dental visits per year; a reduced formulary; quantity restrictions on Zolpidem; and prior approval for atovaquone.

Clearly, the restrictions imposed by the premier ADAP signal tough times for the program nationwide.

Relief for ADAP?

Ardent Advocacy

Across the country, diehard HIV/AIDS activists are feeling the effects of the uphill battle to preserve ADAP. They are tired of pleading for dollars that aren't forthcoming. A tone of despondency, even despair, can be heard resonating in many of their voices. Yet they cannot afford to give up; they've fought too hard and for too long, and the cause is simply too important. Most are personally vested in the cause—they are fighting in remembrance of friends and family members who have died of HIV/AIDS, for the continued quality of life for their close friends living with HIV/AIDS and, in some instances, for their own lives. Their struggle extends beyond preserving a program that may or may not stand the test of time to preserving the quality of life for the thousands of people living with HIV/AIDS.

Bill Arnold, director of the ADAP Working Group, has spent the past 18 years of his life advocating on behalf of people with HIV/AIDS. The ADAP Working Group is a unique ad hoc advocacy coalition comprised of community-based organizations and of biotechnology, pharmacy and pharmaceutical research companies. Once a basement operation, the organization is now at the forefront of a multimillion-dollar effort to save ADAP.

In the beginning, when he received a phone call from one of the clinicians conducting the first protease inhibitor trials, Arnold realized that ADAP would be expected to pay for these newly

tested—and prohibitively expensive—drugs shown to improve the lives of people with HIV/AIDS. He's remained mired in the ongoing hunt for HIV/AIDS treatment funding ever since. "We have a structural deficit of $82 million; I need another $80 million in FY 2003," he says matter-of-factly.

Plotting strategically from the start, Arnold knew what it would take to produce action at the federal level. "The only way to move things in Washington is to bring both sides together—the 'evil' industry and the 'raucous' community.... We've worked from day one to make sure that both industry and community folks are in the room together, making the arguments. That tactic has proven key to avoiding the 'wedge and divide' likely to occur if these two groups were pitted against one another," he says.

> Approximately 900,000 people in the US are living with HIV/AIDS. One in five of those individuals is uninsured.

Arnold's energy and commitment to the cause are clear, and it is leadership like his that has led to the advocacy's success in securing additional ADAP funds thus far. But even the most tireless advocates are getting worn down in the face of persistent funding shortfalls. "I can only walk into offices and ask for a 20 percent increase for so long," Arnold says. What keeps him going at this point is the dread of what might happen if he were to give up.

"If we do nothing, an additional 25,000 to 30,000 people who would have normally come to an ADAP program would not receive treatment.... And people like myself who have been at this for 18 years know that large pools of people not in treatment are bad news. If you're not receiving treatment, you're out there potentially adding to the transmission problem," Arnold says.

Across the country, HIV/AIDS advocates voice similar concerns about the future of ADAP. "It's really rough with our healthcare system so fragmented. Obviously, ADAP was never meant to assist so many people. But it's essential that ADAP is there, and that it's supported, because I don't see that there's an immediate solution," says Donnelly. There are, however, some potential long-term solutions that may ease ADAP's increasingly heavy financial burden.

Pushing for Access to Early Treatment

Some key strategies designed to ease ADAP's burden focus on increased access to early intervention treatment. Leading a few of these pivotal efforts is The Treatment Access Expansion Project (TAEP), a collaborative project of the HIV/AIDS community, healthcare providers, and the pharmaceutical industry.

Presently, TAEP is spearheading the nationwide effort to secure passage of H.R. 2063/S.987, the Early Treatment for HIV Act, or ETHA. This breakthrough act would allow states to extend Medicaid coverage to uninsured, nondisabled people living with HIV. In most states, people with HIV must become disabled by AIDS and meet strict income and asset criteria before they can receive Medicaid coverage.

Logic—and science—tell us that ETHA makes sense. When people receive early access to HAART, they reduce their viral load, slow disease progression, reduce the likelihood of developing opportunistic infections, and increase their overall quality of life.[9] And despite the high cost of HAART, it pales in comparison with the expense of treatment costs at the end stages of the disease.[10] Hence, ETHA would not only promote a higher quality of life for people diagnosed with HIV, but would also reduce considerably the costs associated with HIV/AIDS treatment.

Unfortunately, Capitol Hill's current focus on defense and national security has slowed action on important domestic issues such as increased dollars for HIV/AIDS treatment. But that hasn't deterred TAEP. "We've been meeting with and educating legislators on the bill," says Robert Greenwald, project director for TAEP. For now, the organization's goal is to secure increased—and bipartisan—support of the bill.

TAEP also supports state-based efforts to increase access to HIV/AIDS treatment. One such effort is the push for states to adopt 1115 Medicaid pre-disability waivers that would, like ETHA, allow residents to obtain early intervention treatment via Medicaid. To date, TAEP has assisted several states in submitting HIV waiver applications to the Centers for Medicare and Medicaid Services. Massachusetts was the first state to receive approval of its application. Fully operational, the Massachusetts pre-disability waiver program enrolled over 750 pre-disabled people living with HIV in just its first year. "The moment you test positive for HIV in Massachusetts, you're eligible for Medicaid."

Programs by and for Communities

While some HIV/AIDS advocates work tirelessly to obtain government funding to support treatment, others focus on developing and maintaining programs to meet the treatment needs of their fellow community members.

The Whitman–Walker Clinic, whose flagship clinic is in Washington, DC, is a primary example of the breadth that HIV/AIDS treatment services can encompass when committed people come together and act creatively. Funded by a mix of private and public dollars, the free clinic serves a large client base. In 2001 alone, the clinic treated 11,000 people. On average, patients earn about $15,000 a year. Seventy-five percent are African American; one quarter are women; and a little less than half are heterosexual.

One of the reasons the clinic is so effective is that it has consistently evolved to meet the needs of an ever-changing population. "The focus of Whitman–Walker has not changed, but certainly

the work that we do has changed. We started as a gay and lesbian clinic.... Today, 40 to 45 percent of our population are heterosexual. We continue to develop new programs and services to meet the needs of a changing population. For example, five years ago our pharmacy was not a focus. Today, it is," says Cornelius Baker, executive director of the clinic.

Whitman–Walker's recently established adherence clinic is just one of the many examples of how the organization meets the evolving needs of its clients. The complexity of today's combination therapy, coupled with the adverse side effects that often result from it, make adherence a formidable challenge. Yet patients must maintain strict adherence to their medication regimen to benefit from it. That's why Whitman–Walker uses a team approach to adherence, drawing on the expertise of a nurse, a PharmD, and a physician, each of whom is specially trained to ensure that every patient receives individualized counseling about adherence throughout the treatment process. Other departments that round out the Whitman–Walker Clinic include Case Management, Legal Services, Mental Health and Addiction Treatment, and Vocational Rehabilitation.

Clearly, the staff at Whitman–Walker understand that treating HIV/AIDS effectively requires far more than just providing access to medication. And to date, they've been able to meet the comprehensive needs of the thousands of clients they serve through a combination of private and public funding. But like other treatment programs that rely on government funding, such as ADAP, their future looks uncertain. "We're heavily reliant on public funding. And [in light of the current economic climate] we're just trying to maintain what we have. The reality is that right now we're faced with how we can cut back without doing harm," Baker says.

As public funds for treatment continue at inadequate levels, prevention efforts become more important than ever. "We want to make prevention efforts more effective. To us, it's critical," Baker says. Prevention efforts are so crucial, in fact, that entire organizations have been built around this singular goal. The Stop AIDS Project, founded in 1984 to prevent HIV transmission among gay and bisexual men in San Francisco, is one such organization.

Power of Prevention

In a delicate balancing act, Stop AIDS aims to promote dual "sex positive" and prevention messages. The folks at Stop AIDS take their mission very seriously, incorporating information on the basic science of disease prevention with data from social scientists about people's behavior to create targeted prevention messages. They recently launched a stark, hard-hitting ad campaign intended to counter the misperception that contracting HIV is no longer the grave concern it once was. The ads feature HIV-positive men describing specific adverse side effects of HIV, or of anti-HIV medication—from diarrhea to facial wasting. The ads have struck a chord.

"This is the first thing that's made me think about HIV for a long time," is one comment that David Evans, program director of Stop AIDS, has heard repeatedly since airing the ads. Another response demonstrating the ads' impact was this: "My God, somebody's finally telling the truth."

This feedback demonstrates the campaign's effectiveness. "Many men say to us that while trying to give hope to folks who are positive, we've painted such a rosy picture that many folks have picked up the message that HIV is no longer a big deal," Evans says. And as anyone living with HIV will tell you, that's just not true.

Ads such as those sponsored by Stop AIDS may help to convince legislators and the public at large that the HIV/AIDS epidemic remains a "big deal." What's more, it will become an even bigger deal if funding for programs like ADAP and others that aim to prevent and treat HIV and its transmission continue to come up short.

Unfortunately, problem situations often go unrecognized until they reach a crisis point. Yes, the bridge that ADAP was created to form is buckling in many areas. But unless it breaks down completely, resulting in thousands of people being denied life-saving drugs, there's a very real possibility that little will be done to fix it.

As Bill Arnold so aptly observes: "In the American political system, there's no real problem until it's on the front page and the evening news. Then it's thousands of people damaged.... But you won't be able to repair the damage to the thousands of people who end up creating the headlines."

Elizabeth Heubeck is a Baltimore-based freelance writer who frequently writes on health issues. N

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AMERICAN ACADEMY OF HIV MEDICINE

JUDITH FEINBERG, MD, BOARD CHAIR, AAHIVM

Over the past few years, the American Academy of HIV Medicine has established a national standard of care for HIV patients in the United States. The Academy believes that this national standard improves the quality of care for HIV patients by ensuring that HIV providers maintain up-to-date knowledge about HIV treatments. The Academy maintains a listing of HIV Specialists at its website: www.aahivm.org.

Improving the Quality of HIV Care

HIV is a complicated disease, and the paradigm for treating HIV shifts frequently. Developments have occurred over the last year that have completely reversed established thinking about the disease. As HIV and the drugs used to treat it have evolved, it has become clear that this is a disease that must be managed by an HIV Specialist.

The Academy believes that because the criteria it uses to define an HIV Specialist also define the optimal standard of care for HIV patients, defining what it means to be an HIV Specialist will improve treatment outcomes in individuals with HIV. HIV Specialists can better recognize, diagnose, treat, and effectively manage the medical complications of HIV disease with current treatment modalities and state-of-the art drug therapies. HIV patients also can be assured that their provider has maintained a level of competency that is recognized by the healthcare industry.

The Academy's definition of an HIV Specialist addresses the three essential elements that demonstrate professional development: education, experience, and external validation. External validation is established through a self-study exam that is completed by providers when they apply for a credential. The exam evaluates whether a provider's knowledge about HIV care is up-to-date.

The Academy also requires that HIV providers who wish to be considered HIV Specialists meet these qualifications on a regular basis. Continuing evaluation of an HIV provider's knowledge ensures that patients are cared for by providers with up-to-date information about treatment, increasing the quality of care that patients receive.

Improving the quality of care for HIV patients has tremendous potential to improve treatment outcomes and quality of life and may also increase the cost-effectiveness of patient care. The Academy has worked to improve the quality of HIV care by:

- Establishing a national standard of care through its Core Curriculum, a list of more than 200 Learning Objectives that together define the minimal knowledge needed to qualify as an HIV Specialist
- Creating and sustaining an HIV Specialist credentialing process to recognize HIV medical providers who possess up-to-date knowledge about HIV care
- Providing vital tools for HIV medical providers including patient handouts, conference listings, and practice management information
- Organizing advocacy and educational efforts for HIV medical care providers at national and state levels

Improving Access to Quality HIV Care

The Academy believes that HIV/AIDS patients should have access to the quality care provided by a competent HIV Specialist. AIDS organizations receive a large number of inquiries daily from patients needing referrals for HIV providers. Often, they refer patients to county medical societies, general physician listings, or other provider lists. Unfortunately, few of these organizations require anyone to meet a set of standards in order to be listed on these referral lists. As a result, some patients are receiving substandard care even from experienced providers.

The Academy encourages patients to ask their providers whether they are credentialed as an HIV Specialist through the Academy. This will ensure patients that their provider possesses the critical knowledge needed to provide quality care. The Academy also encourages health systems, hospitals, clinics, and individual medical practices to use HIV providers who demonstrate and maintain competency in HIV medicine.

The Academy has made efforts to help to lower entry barriers into HIV medicine by:

- Centralizing critical educational resources and assembling and continually updating a study guide containing clinical and factual data for the entire Core Curriculum
- Maintaining a searchable national listing of HIV healthcare providers and credentialed HIV Specialists at its website to link HIV patients to qualified providers
- Continuing to work to ensure the viability of HIV practices to maintain and expand access to health care
- Lowering entry barriers to the field through various programs including the creation of a national Job Bank specifically for professionals in HIV care

Finding a Provider

The Academy maintains the only national listing of HIV Specialists who have met the national standards that it has established. As mentioned above, credentialed providers are listed at the Academy website (www.aahivm.org) to help link patients and service providers to qualified HIV Specialists.

Using the search for a provider feature, patients may search for a provider by name or by location using a zip code search. Contact information, office hours, and types of insurance accepted are listed for many providers.

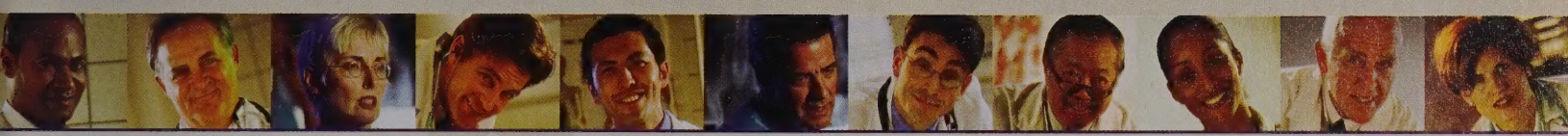
To access the search for a provider feature, visit the Academy website at www.aahivm.org and click on "Find a Provider," located on the left-hand side of the screen. For help or more information about the Academy, contact us by telephone toll-free at 866-241-9601 or by e-mail at info@aahivm.org.

About the Academy

The American Academy of HIV Medicine is an independent organization dedicated to promoting excellence in HIV/AIDS care. Through advocacy and education, the Academy has committed itself to supporting healthcare providers in HIV medicine and to ensuring better care for those living with AIDS and HIV disease.

Judith Feinberg, MD, is Professor of Medicine at the University of Cincinnati College of Medicine, Cincinnati, Ohio. She is Principal Investigator of the University of Cincinnati AIDS Clinical Trials Unit and has served as a member of the AIDS Clinical Trials Group (ACTG) Executive Committee, and as Vice-Chair and then Chair of the ACTG Opportunistic Infections Committee. She has served on the U.S. Food and Drug Administration's Antiviral Drugs Advisory Committee, and the Public Health Service Guidelines Task Force, and is an Associate Editor of AIDS Clinical Care and Infectious Diseases in Clinical Practice.

The American Academy of HIV Medicine



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Innovative Teaching Strategies for HIV Disease Faculty Development Institute: Caring Hands

ADELE A. WEBB, PHD, RN, ACRN, FAAN, EXECUTIVE DIRECTOR, ANAC

Those of us deeply involved in HIV care have had many concerns about the education of nursing students related to the epidemic, and our research has revealed that these concerns were well grounded. Students were graduating with inadequate preparation to care for patients living with HIV/AIDS. In response to this concern, the Association of Nurses in AIDS Care (ANAC) created a Faculty Development Program to assist faculty as they struggled to prepare their students for the inevitable HIV patient. This effective program was well received and well attended; it brought sound information about HIV disease to faculty across the United States.

We would like to think that things have improved—that more and more faculty are prepared to teach complex HIV content to their nursing students. However, the evidence points to the contrary. In many institutions, nursing school curricula provide little information about caring for those with HIV disease. Faculty self-report little to no personal experience with the disease, and this makes them hesitant to assign their students to often complicated HIV patients. Nursing students continue to end their training with fear, anxiety, and feelings of vulnerability about HIV-related nursing care.

The Association of Nurses in AIDS Care has responded to this issue. A revised Faculty Development Program has been developed that has as its purpose *to enhance the ability of nursing faculty to teach students about the spectrum of HIV disease in populations across the lifespan.* The ultimate goal of the course is to increase knowledge about HIV infection, to enhance skill development in this and in related areas, and to improve nursing care for HIV-positive clients. The course emphasizes the importance of incorporating HIV-related content into the curriculum and will provide information about how to successfully integrate this content into existing curricula.

This program, held in St. Louis, MO, April 4–6, 2003, offered nursing faculty a unique opportunity to come to the table to learn about HIV disease and to share their ideas about innovative strategies for presenting difficult content to their students.

The program is designed to enable nursing faculty to:

- Educate nursing students about current concepts of care for patients with HIV disease
- Use innovative teaching strategies to teach key concepts about HIV infection across the curriculum
- Integrate information about HIV infection into appropriate components of the curriculum

In addition to the content provided by ANAC member clinicians and educators, the program incorporated a poster session that displayed refereed posters related to innovative nursing education strategies. The authors were available to discuss how to adapt the innovative strategies to HIV content presentation.

Jerry Durham, PhD, RN, FAAN, the keynote speaker, set the stage for the program with his address, Nursing and the HIV Pandemic: Two Decades of Caring. Because of Dr. Durham's expertise in HIV nursing and his plethora of publications, this address is expected to be both informative and exciting.

ANAC will provide teaching tools to conference participants, including a CD-ROM that contains slide presentations and abstract submissions, creative teaching strategies, articles, and handouts.

For additional information please contact Ginger Pesata, FacDev@anacnet.org, or go to ANAC's website at: www.anacnet.org.

Adele Webb, PhD, RN, ACRN, FAAN, is a past President of the Association of Nurses in AIDS Care (ANAC). Currently, Dr. Webb serves as ANAC's Executive Director. N

ABOUT ANAC: HISTORY AND MISSION

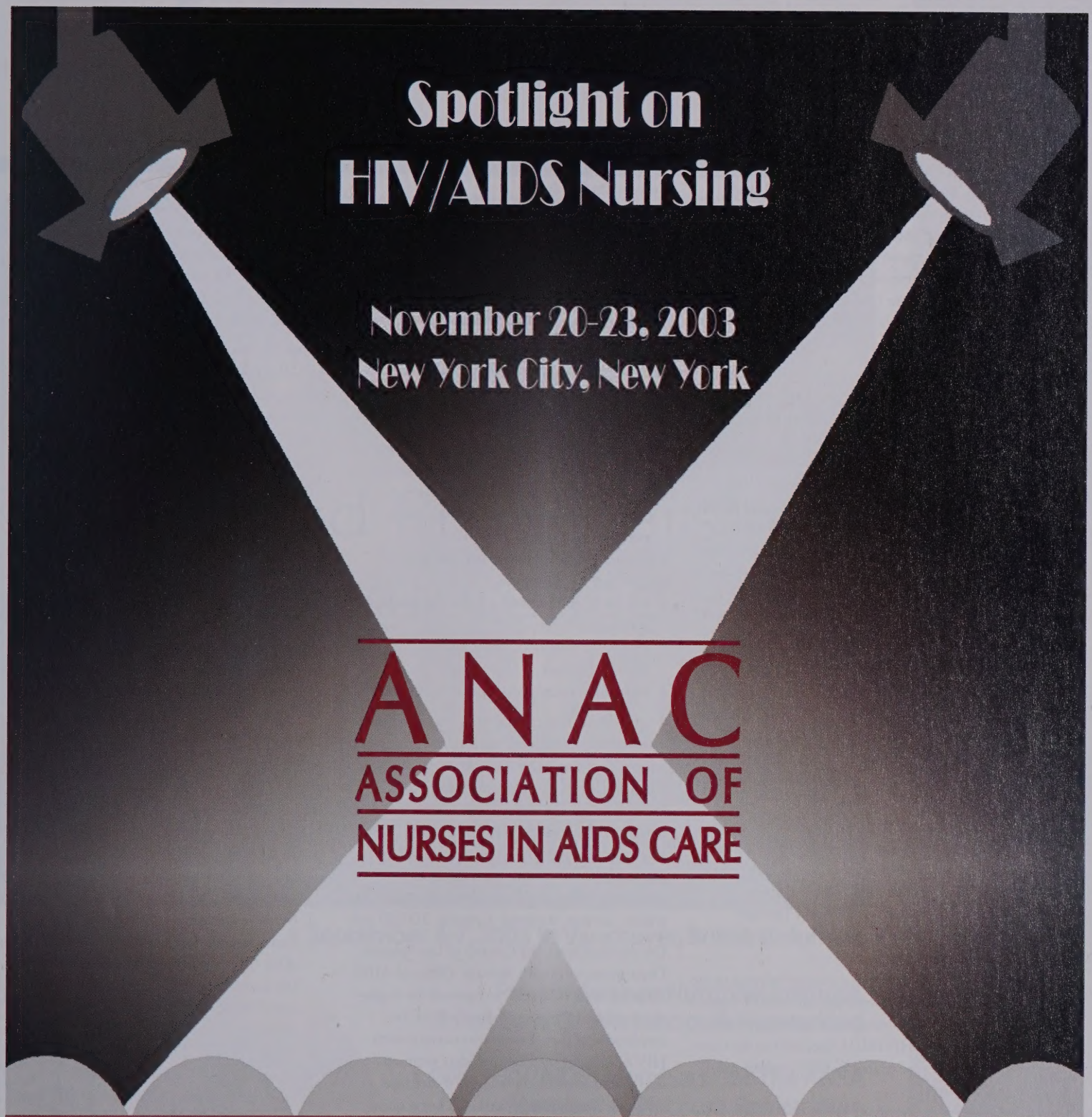
The Association of Nurses in AIDS Care is a nonprofit professional nursing organization committed to fostering the individual and collective professional development of nurses involved in the delivery of health care to persons infected or affected by the Human Immunodeficiency Virus (HIV) and to promoting the health, welfare, and rights of all HIV infected persons.

The members of ANAC strive to achieve the mission by:

- Creating an effective network among nurses in HIV/AIDS care
- Studying, researching and exchanging information, experiences, and ideas leading to improved care for persons with AIDS/HIV infection
- Providing leadership to the nursing community in matters related to AIDS/HIV infection
- Advocating for HIV infected persons
- Promoting social awareness concerning issues related to HIV/AIDS

Inherent in these goals is an abiding commitment to the prevention of further HIV infection.

Sixteenth Annual ANAC Conference



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Screen for Dietary Needs and Refer On

MARCY FENTON, MS RD

"It is necessary for the patient to be entered into a continuum of medical care and services, including social, psychosocial, and nutritional services, with the availability of expert referral and consultation." These clear directions are found in the conclusion of the Department of Health and Human Services' Guidelines for the Use of Antiretroviral Agents in HIV-infected Adults and Adolescents,[1] which have been unaltered since they were first published in 1998.

The intent mirrors the joint positions of the American Dietetic Association and Dietitians of Canada, first published in 1994, that "...efforts to optimize nutritional status, including medical nutrition therapy and nutrition-related education, should be components of the total health care provided to people infected with human immunodeficiency virus (HIV)."[2] In November 2002, the State of California issued final regulations defining the HIV/AIDS Specialist, to ensure implementation of AB 2168 (Chapter 426, Stats. 2000), which specifies that any HIV-infected patient covered by managed care be referred to an HIV Specialist.

In March 2002, the HIV/AIDS Dietetic Practice Group (DPG) recommended to the State of California Department of Managed Health Care that the proposed regulation include the following additions[3]:

- Require the HIV/AIDS Specialist to refer to registered dietitians as specified by the Los Angeles County Commission on HIV Health Services' Guidelines for Implementing HIV/AIDS Medical Nutrition Therapy Protocols.[4] This includes when, why, how, and to whom to refer.
- Ensure that registered dietitians referred to are competent and knowledgeable in HIV nutrition and can communicate with the patient.
- Require the HIV/AIDS Specialist to earn one CME per year related to HIV medical nutrition therapy.
- Require the certifying agency to include in its core curriculum, study guide, and exam how to identify nutrition-related problems and when and how to refer to registered dietitians for medical nutrition therapy.

In addition to providing input into regulations, the HIV/AIDS DPG pursued the issue by working directly with the American Academy of HIV Medicine (AAHIVM), an organization identified to credential an "HIV Specialist" under the State of California final regulation.

The HIV/AIDS DPG Education Subcommittee developed a proposal[5] for the AAHIVM's Core Curriculum Faculty to:

- Establish a separate objective on HIV nutrition
- Identify nutrition-related problems for adults using a comprehensive screening tool
- Provide referral for medical nutrition therapy
- Recognize qualifications of registered dietitians to better ensure competency in HIV nutrition

The proposal and related documents are posted online at www.hivaidsdpg.org/publicpolicy/specialist.aspx.

Nutrition-related problems that would trigger an immediate referral to a registered dietitian are categorized into six areas:

- New diagnosis, any status change, or no assessment in the last 6 months
- Physical changes and weight concerns
- Oral and GI symptoms
- Metabolic complications and other medical conditions
- Barriers to nutrition, living environment, and functional status
- Behavioral concerns or unusual eating behaviors

The screening and referral form was developed in collaboration with the working group engaged in updating the Adult HIV/AIDS Medical Nutrition Therapy Protocol, part of the American Dietetic Association's Evidence-Based Guides. The screening and referral form is available at the HIV/AIDS DPG website address previously mentioned or directly at www.hivaidsdpg.org/Data/QM/HIV_Adult_Nutrition_Screen_Referral_Criteria_200207.pdf.

On the local level, the County of Los Angeles Department of Health Services' Office of AIDS Programs and Policy has recognized the importance of nutrition as a primary part of the continuum of care. Last year's contracts with HIV outpatient medical providers required nutrition counseling by registered dietitians. This year's contracts go further. They require screening for nutrition-related problems with a new diagnosis, with any status change, **and** at least every 6 months with appropriate referral to a registered dietitian. The contract identifies the six categories listed above for referral to a registered dietitian for medical nutrition therapy. In addition qualifications for the registered dietitian are specified.

The HIV/AIDS Dietetic Practice Group (DPG), formed in 1997, has been advocating continuously through public policy and education for the integration of nutrition into HIV disease management. The HIV/AIDS DPG leadership is proud of the years of work and collaborations that have brought us to this milestone and closer to comprehensive care for all people living with HIV disease. We recognize that we must continue to work locally as well on the state and national levels.

Janelle L'Heureux, MS RD chaired the HIV/AIDS DPG Education Subcommittee, which included Susan Basinger, RD, Eva Brzenzinski, MS RD, Carol Capozza, MS RD CNSD, Marcy Fenton, MS RD, and Monica Randel, RD. The Adult HIV/AIDS Medical Nutrition Therapy Protocol working group consisted of Kristen Coyne, RD CDE, Sherry Lassa-Claxton, MS RD, Tammy Darke, RD CNSD, Marcy Fenton, MS RD, Janelle L'Heureux, MS RD, and Ellyn Silverman. MPH RD.

Marcy Fenton is the current Education Chair of the HIV/AIDS Dietetic Practice Group and a nutritionist in the HIV Nutrition Education Program of AIDS Project Los Angeles. She can be reached at (213) 201-1611 or at mfenton@apla.org. N

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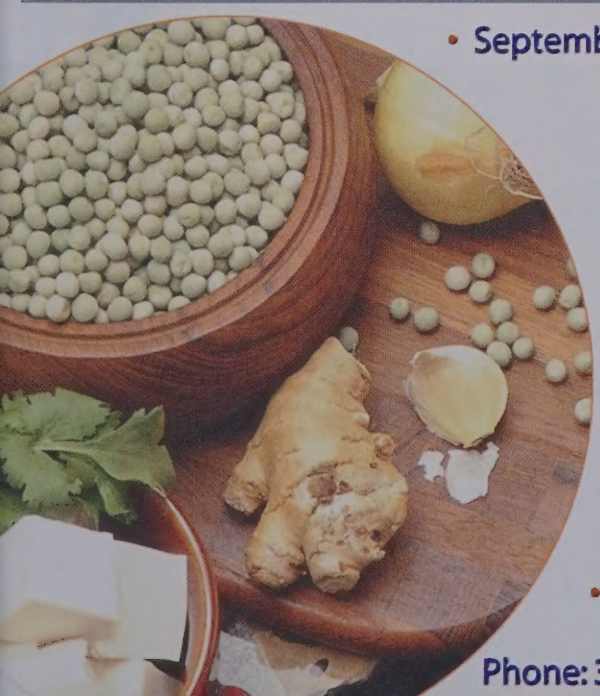

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HIV Over Age 50

MICHELLE McGRAW, RPH, MANAGER OF CLINICAL PHARMACY PROGRAMS, CVS PROCARE

The death of Rock Hudson in 1985 not only put a face to the AIDS epidemic and brought discussion about this disease into our living rooms, but also demonstrated that AIDS does not discriminate based on age. It is important for the medical community and for society to recognize the potential for HIV infection in an older population and to promote educational programs and discussions geared towards patients over age 50. While there have been many initiatives developed in an effort to educate today's youth about the dangers of unprotected sex and the risk of transmission of HIV, and safer sex lectures are now commonplace in the world of today's teenager, we hear very little about the education of an older population. The lack of education targeted to this group of older patients may be perpetuating the myth that HIV is a young person's disease.

Americans over age 50 account for a rising percentage of the HIV population. In the early 1990s, patients over 50 accounted for approximately 10 percent of the HIV population. By 1999 that number had increased to 13.4 percent; in some areas the percentage of HIV patients over 50 is believed to be as high as 15 percent.[1] The greatest increase in HIV cases of people over 50 has occurred in women. The National Institute on Aging reported that over a recent 5-year period, the number of new AIDS cases in women of this age group increased by 40 percent.[2] From 1991 to 1996, AIDS cases rose twice as fast in the over-50 population as they did in younger people. The combination of limited HIV education in this age group, an aging HIV population due to the development of better therapies, and an increase in patients of this age group reporting IV drug use are all factors influencing the increased incidence of the disease in the over-50 population. Some of these patients may have contracted the disease several years ago, but development of symptoms may have been delayed. Most of these infections are believed to be linked to sexual activity; the heterosexual HIV transmission rate is higher for this age group than for any other.[3]

These statistics discount the common misconception that older people are not sexually active and are therefore not susceptible to contracting HIV. In fact in 1999, the American Association of Retired Persons (AARP) conducted a study of 1,384 adults and found that more than half of men and women aged 45 to 59 reported that they had sex at least once a week. They further noted that one fourth of men and women over age 75 have sex at least once a week.[4] These facts need to be stressed to healthcare practitioners who may not consider the necessity of asking an older patient about previous and current sexual activity. It is unfortunate that this patient population is often overlooked when considering the potential risk of HIV and the need for HIV testing.

They may also be overlooked when education and prevention programs are developed. Older people frequently know less about HIV and how it is transmitted than other people do. Older patients, also believing this to be a young person's disease, may not consider themselves at risk and therefore may not discuss risky behavior with physicians.

Seniors have lived most of their lives at a time when AIDS was not known and rigorous safer sex practices were not as important as they are today. Many of them have had sex only with their spouse and are not accustomed to safer sex practices or discussions about condom use with their partner or a health practitioner. Postmenopausal women, no longer at risk for pregnancy, are less likely to consider the use of condoms. Women over age 50 experience thinning of the vaginal walls and vaginal dryness; such physical changes can result in increased risk of abrasions and tears and therefore an increased risk of disease transmission. All of these factors occur at a time when immune system function is on the decline. There are few studies comparing survival rates of younger and older HIV patients, but there is some evidence that elderly HIV patients may die sooner once diagnosed, possibly because older patients are often not diagnosed until later in the progression of the disease and because the HIV diagnosis may be complicated by concurrent conditions.

To complicate matters, HIV symptoms often mimic symptoms of aging. Fatigue, memory loss, and digestive problems associated with HIV can often be attributed to the aging process. Symptoms of HIV dementia may be mistaken for Alzheimer's or Parkinson's disease. HIV symptoms might easily be misdiagnosed as symptoms of the normal aging process.

Once diagnosed, treatments for HIV can lead to adverse events, which expedite the aging process. Protease inhibitors (PIs) may be associated with blood glucose changes leading to diabetes, and may also be associated with increased cholesterol levels. Nucleoside reverse transcriptase inhibitors (NRTIs) have been associated with anemia, neutropenia, and damage to the mitochondria, causing fatigue, muscle wasting, and neuropathies. In some instances, complications associated with the use of these drugs, such as diabetes or increased cholesterol, can contribute to the cause of death for these older patients.

The use of these HIV therapies has not been adequately studied in patients over age 65. Very little is known about dose-adjustment requirements. More importantly, there is also insufficient data concerning potential drug interactions between HIV therapies and other drug therapies commonly used by this older patient population, such as antihypertensives, diabetic medications. and cholesterol-lowering agents. It is known that protease inhibitors and the non-nucleoside reverse transcriptase inhibitors (NNRTIs) are primarily metabolized by CYP3A enzyme systems. Although drug interactions may not be documented, careful review of factors including enzyme system involvement, metabolism, and excretion pathways should be considered for potential interactions with other agents.

All of these factors can make recognizing and treating the mature HIV patient more challenging. It is important for all practitioners to recognize the need for proper education for this patient population in order to limit the risk of transmission. A behavior modification suggestion to keep condoms on the bed table may be more effective than education alone. Discussions surrounding HIV risk factors should be considered for all patients and should not exclude patients often thought of as not at risk. Discussions should include taking sexual histories and counseling for patients at risk for transmission of HIV.

Pharmacists, also, should be sensitive to the potential for HIV infection in the aging population. Because they often have more frequent contact with patients than primary physicians do, pharmacists may often be the first to recognize symptoms that require treatment. Pharmacists should also be sensitive to the potential for drug interactions between HIV therapies and other agents, and they can provide counseling about the importance of safer sex practices to patients receiving treatment for sexual dysfunction or vaginal dryness.

Additional information about the prevention and treatment of HIV infection is available through multiple sources including the National Institute on Aging, the National Association of HIV Over Fifty (NAHOF), and Senior Action in a Gay Environment (SAGE). The NAHOF will be conducting the 4th National Conference on HIV/AIDS and Aging on September 5–6, 2003.[5]

Consideration by the medical community of the rising incidence of HIV in patients over age 50 is vital. Specialty pharmacists trained to consider the specific needs of HIV patients will become increasingly important to the monitoring and care of older HIV patients with concurrent medical conditions. Working together, healthcare workers, using a multidisciplinary approach to care, can help improve the education and care of an aging HIV population.

Michelle McGraw, RPh, is a manager of clinical pharmacy programs for CVS ProCare Pharmacy.

Editor's Note: Please see the related articles on the organization SAGE and on HIV in older adults elsewhere this journal.

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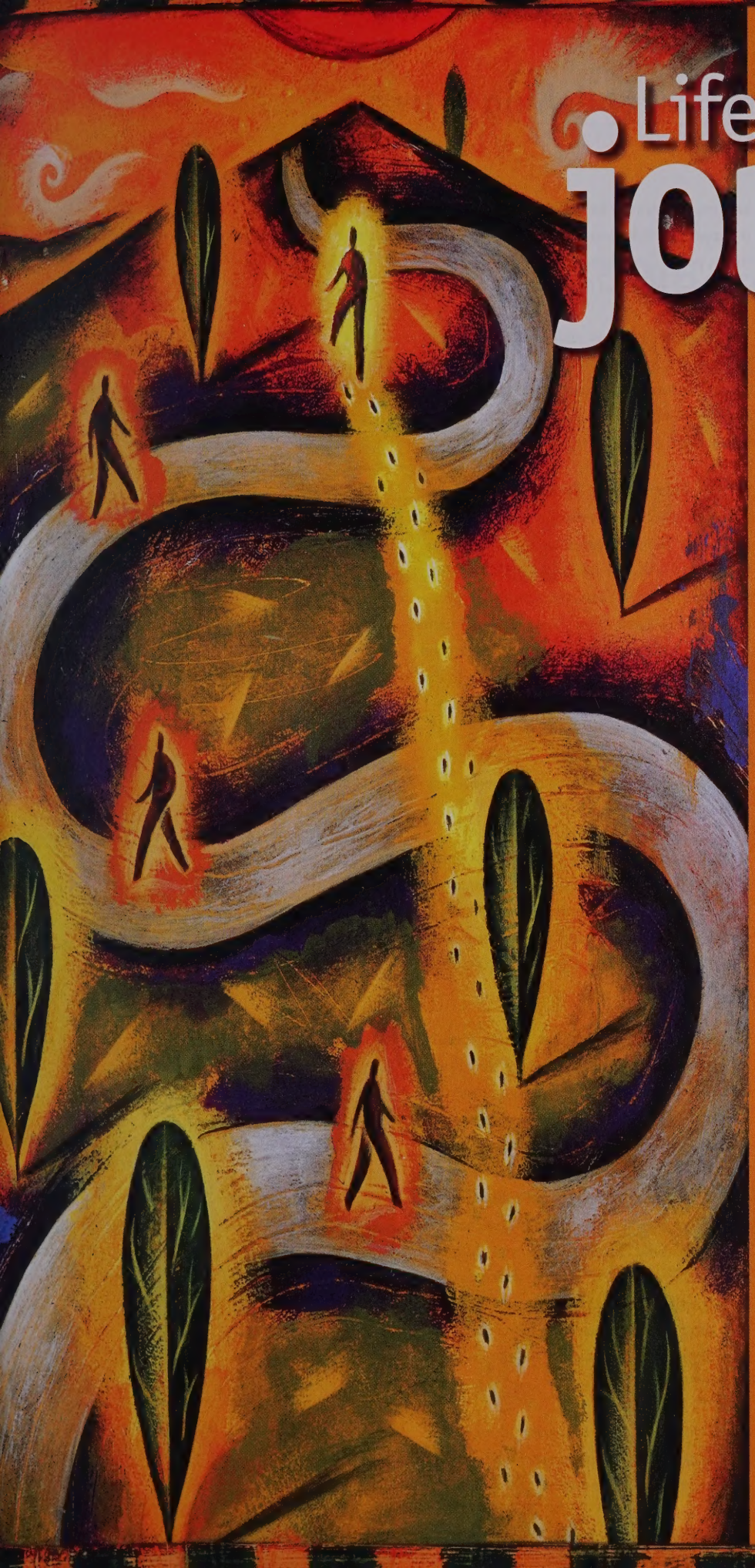

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Leave a Lasting Legacy: Establishing a Living Trust

DAVID WEIGEL, SENIOR VICE PRESIDENT – INVESTMENTS, UBS PAINEWEBBER, INC

You've worked hard all your life for your money, and you've worked hard at taking care of it. But do you really know what will happen to what you've accumulated after you die?

The fact is that if you don't plan properly now, your estate could be eroded by estate taxes. In addition, subjecting your estate to probate—the legal process through which the court ensures that upon your death, your debts are paid and your property is distributed according to your will—may mean additional costs and delays in transferring assets to your heirs. So, if you want your estate to go to your heirs instead of to the IRS, plan carefully now.

Estate planning has three basic goals. The first is to minimize estate expenses and taxes. The second goal is to make provisions in advance for meeting these expenses so that your estate is not forced to liquidate assets in a "distress" sale environment. The third goal of estate planning is to make sure that the distribution of the remaining assets to your heirs is orderly and according to your wishes. Estate planning is essential since the first payments made from an estate are for estate expenses and estate taxes; your heirs actually receive what is left.

Many people believe that a will is the best way to plan for the distribution of their estate, but this is not always true. A will does not avoid probate, and, because a will can go into effect only after you die, it provides no protection for you and your heirs if you become disabled.

What Is So Bad About Probate?

The probate process can be an expensive and time-consuming process, depending on the state where you live. Probate costs, which must be paid from your estate before anything can go to your heirs, are generally estimated at 5 percent of an individual's gross estate value, and can be even higher in some cases. The probate process can take one to two years, or longer in some states.

In addition, during probate your family loses control of your estate, as well as privacy. The probate process—not your family—has control, and your assets may be tied up until this process is completed. Additionally, probate files are open to the public, so anyone can get information about your assets and liabilities.

Fortunately, there is an alternative to wills and probate. It's called the **revocable living trust**. It avoids probate, and it ensures your estate plan won't be altered by the court or legal technicalities in the event of your death or disability.

What Is a Living Trust?

If you establish a trust during your lifetime, it is called a "living" trust. It's a legal document similar to a will, but offers much more. When you set up a living trust, you simply transfer most of your assets from your individual name to the name of your trust—which you control. Since there is no probate process with a living trust, upon your death, your assets are transferred to your heirs. All expensive court proceedings and delays are eliminated, your privacy is preserved, and the emotional stress on your family is minimized.

If you have a modest estate and your trust is fairly simple, you may be just fine as your own trustee. However, if your estate is larger, has a variety of assets, or requires tax planning, you should probably consider having a professional trustee involved.

Most people select a corporate trustee as their successor or co-trustee, especially if they don't have the time, ability, or desire to manage their own trust, or if one or both spouses are in declining health. Corporate trustees are in the business of managing trusts—they're experienced investment managers and trained to be objective. Their fees are generally competitive and if something happens to you, your corporate trustee will continue to manage your trust for you according to your instructions. If you and your spouse are co-trustees, either can act and instantly take control if one becomes disabled or dies.

If you die or become incapacitated, or if you are the only trustee, the trustee you selected can automatically step in and take over for you. This successor trustee looks after your care and manages your financial affairs for as long as necessary, using your assets to pay your expenses.

How Is a Living Trust Established?

You make the basic planning decisions—inventory your property, decide who will be your beneficiaries, select your successor trustee, name a trustee and guardian for minor children, etc. Your attorney then prepares the actual legal document that addresses your specific needs. You sign the trust document, it is notarized, and then you change most of your property titles to reflect the name of your trust. You should also change beneficiary designations on appropriate assets.

Customizing Your Estate Plan

Many investment firms have wealth preservation programs designed to help secure the continued growth of your hard-earned assets and enhance your family's future. These programs can provide referrals to estate planning attorneys and professional trust consultants whose advice and counsel are necessary in helping you customize a plan according to your specific needs. A plan can help you protect the assets you've spent a lifetime accumulating so that you not only provide for the future financial needs of your heirs, but leave a lasting, fulfilling legacy for years to come.

UBS PaineWebber does not provide tax or legal advice. You must consult with your attorney and tax adviser regarding your specific situation.

Editor's Note: The NUMEDX Financial Network's primary mission is to bring cutting-edge information on both the personal and fiscal implications of the HIV/AIDS epidemic.

"Wherever the art of medicine is loved, there also is love of humanity."

Hippocrates

UBS PaineWebber salutes the strength and vitality of people living with AIDS, HIV, and hepatitis.

We recognize the dedication of the medical community for its achievements in treatment, prevention, and education.

David W. Weigel
Senior Vice President-Investments

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Physician Assistant AIDS Network (PAAN): Year in Review

MARY ADAIR, PA-C, NATIONAL COORDINATOR, PAAN

The Physician Assistant AIDS Network (PAAN) has been very busy over the past year. The President of PAAN went to Africa to help initiate HIV treatment in Masaka, Uganda, and Durban, South Africa. Currently, 200 Africans are receiving life-saving antiretroviral (ARV) medications with support from AIDS Healthcare Foundation's program, Global Immunity. Medications began February 15, 2002—so far, there has been only one death; all other patients have maintained good health, returned to work, and have increased CD4 counts. Not one patient has missed one dose of medications.

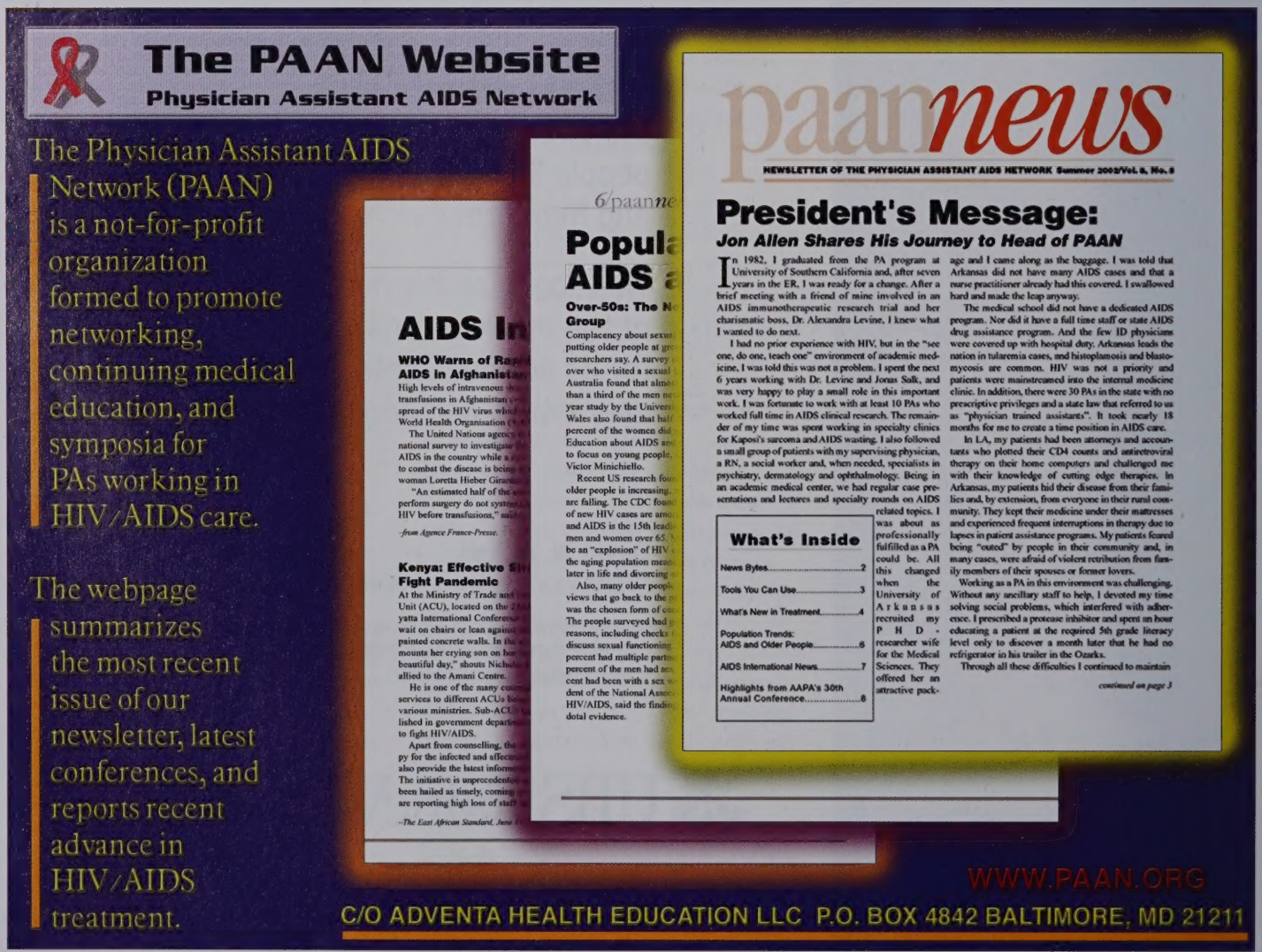
The PAAN web site, www.paan.org, has been updated and has lots of new features, including a job board. The quarterly newsletters are now online.

Last year, we held our PAAN conference in conjunction with the American Academy of Physician Assistants in Boston, Massachusetts. It was a great success. During our conference, we elected a new President, Jon Allen, PA-C from Little Rock, Arkansas. Jon has been a PAAN board member since 1997 and brings experience in organizational development. He was a leader in Arkansas in getting prescription privileges for PAs.

Planning has begun for our yearly HIV CME activity at the National PA conference, to be held in New Orleans in May 2003. We have planned our CMEs this year to reach all PAs interested in HIV/AIDS as well as advanced clinicians. Our CMEs will cover areas such as dermatology, co-infection with hepatitis C, sequencing of antiretrovirals, and what's new in the pipeline.

PAAN is dedicated to keeping its members and the public educated about HIV/AIDS issues throughout the world.

Mary Adair, PA-C, is a physician assistant with the AIDS Health Care Foundation and National Coordinator, Physician Assistant AIDS Network, Los Angeles, CA. For information on clinical rotations in Africa, contact the author at: paanmarya@aol.com.


The PAAN Website
Physician Assistant AIDS Network
The Physician Assistant AIDS Network (PAAN) is a not-for-profit organization formed to promote networking, continuing medical education, and symposia for PAs working in HIV/AIDS care.
The webpage summarizes the most recent issue of our newsletter, latest conferences, and reports recent advance in HIV/AIDS treatment.
paannews
NEWSLETTER OF THE PHYSICIAN ASSISTANT AIDS NETWORK Summer 2002/Vol. 6, No. 3
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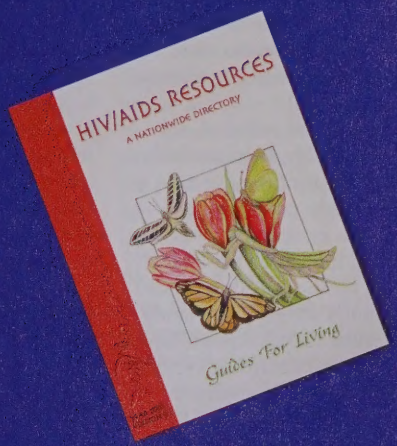

When your goal is to help HIV/AIDS patients, navigating the vast amounts of information can be like searching for a needle in a haystack. Truth is, you've got better things to do than searching for services in other areas of the US.

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FDA APPROVES NEW RAPID HIV TEST KIT

HHS Secretary Tommy G. Thompson today announced that the U.S. Food and Drug Administration has approved a new rapid HIV diagnostic test kit that provides results with 99.6 percent accuracy in as little as 20 minutes.

Using less than a drop of blood collected, this new test can quickly and reliably detect antibodies to HIV-1, the HIV virus that causes infection in most cases in the U.S. Unlike other antibody tests for HIV, this test can be stored at room temperature, requires no specialized equipment, and may be considered for use outside of traditional laboratory or clinical settings. The newly approved HIV test is called The OraQuick Rapid HIV-1 Antibody Test, manufactured by OraSure Technologies, Inc., Bethlehem, Pennsylvania.

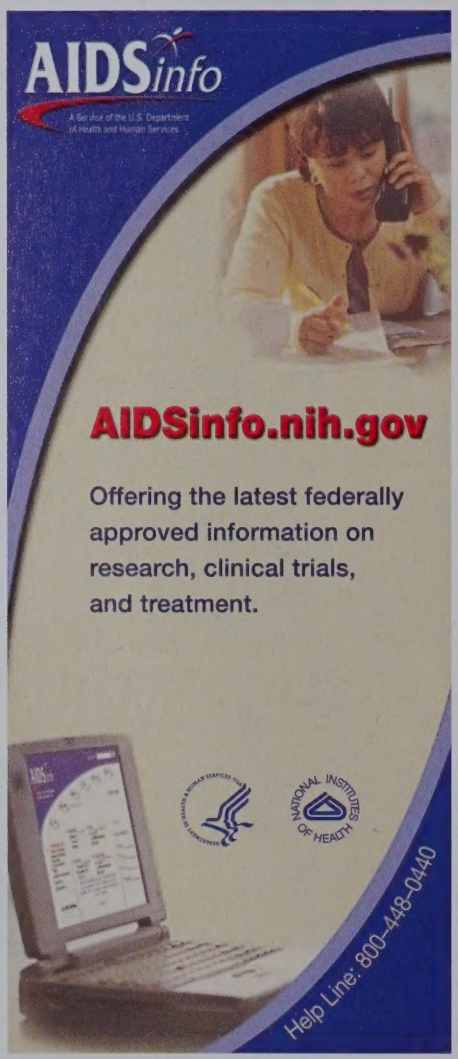
"Each year, 8,000 HIV-infected people who come to public clinics for HIV testing do not return a week later to receive their test results," Secretary Thompson said. "With this new test, in less than a half an hour they can learn preliminary information about their HIV status, allowing them to get the care they need to slow the progression of their disease and to take precautionary measures to help prevent the spread of this deadly virus."

To perform the test, a fingerstick sample of blood is collected from an individual and transferred to a vial where it is mixed with a developing solution. The test device, which resembles a dipstick, is then inserted into the vial. In as little as 20 minutes, the test device will indicate if HIV-1 antibodies are present in the solution by displaying two reddish-purple lines in a small window on the device. Although the results of rapid screenings will be reported in point-of-care settings, as with all screening tests for HIV, if the OraQuick test gives a reactive test result, that result must be confirmed with an additional specific test. The OraQuick test has not been approved to screen blood donors.

FDA currently categorizes the OraQuick test as "moderate complexity" under the Clinical Laboratory Improvements Amendments of 1988 (CLIA). Under CLIA, new tests are categorized as either moderate or high complexity. This designation means that the OraQuick test can only be given in CLIA-approved labs by CLIA-certified laboratory technicians or medical staff. If the test manufacturer applies for a CLIA waiver, the FDA can evaluate it for use under less stringent conditions.

"I strongly urge the OraSure company to apply for a CLIA waiver," said Secretary Thompson. "If the FDA finds that the company's data proves that the OraQuick test is both easy and safe to use, it can get a CLIA waiver. Then the test could be given in many more health care settings, perhaps even administered by social workers in HIV counseling centers. But the process can't begin until OraSure applies for the waiver, so I ask them to please apply now!"

The Centers for Disease Control and Prevention (CDC) has estimated that one fourth of the approximately 900,000 HIV-infected people in the U.S. are not aware that they are infected. Because of the potential public health benefits of rapid HIV testing, the CDC and the Centers for Medicare and Medicaid Services (CMS) are working with state and other health officials to make the test widely available and to offer technical assistance and counseling training for its use.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"This test will be a great help in identifying pregnant HIV-infected women going into labor who were not tested during pregnancy so that precautionary steps can be taken to block their newborns from being infected with HIV," said FDA Deputy Commissioner Dr. Lester M. Crawford. "It will also be a critical resource in emergency workers who are accidentally exposed to HIV-infected blood while doing their job."

Editor's Note: A CLIA waiver has been granted for the use of this test.

Source:
www.fda.gov/bbs/topics/NEWS/2002/NEW00852.html. Date Accessed December 02, 2002

FDA APPROVES NEW FORMULATION OF ZERIT

The Food and Drug Administration has approved a new, extended release formulation of Zerit® (stavudine, d4T) called Zerit® XR. This extended-release formulation has been demonstrated to maintain measurable plasma concentrations for 24 hours after once-daily dosing. Zerit XR is indicated for the treatment of HIV in combination with other antiretrovirals. The recommended dose is 100 mg once daily for individuals weighing at least 60 kg and 75 mg once daily for individuals weighing less than 60 kg.

GONORRHEA TEST KITS RECALLED BY ABBOTT LABORATORIES

The Food and Drug Administration (FDA) today announced that Abbott Laboratories, Inc., has initiated a worldwide recall of 32 lots of laboratory kits used to diagnose gonorrhea. The kits have been shown to be unreliable because they may give false negative results. These test kits were distributed to hospitals and laboratories from Jan. 11 to June 24, 2002.

Gonorrhea is a serious, highly contagious sexually transmitted disease that affects both men and women. Women primarily suffer severe consequences from infection that is not detected and treated. Untreated gonorrhea in women can cause pelvic inflammatory disease that can lead to sterility. In pregnant women, infection can potentially cause abortion, premature delivery, or infection in the baby. If undetected and untreated in men, it can cause an infection of the urethra that makes urination painful and difficult. In both sexes, infection can spread through the bloodstream and infect the joints, skin, bones, tendons and other parts of the body.

"FDA is alerting the public to this recall to help protect the public health," said FDA Deputy Commissioner Lester M. Crawford. "We want to make sure laboratories that have purchased these test kits, physicians who have ordered these tests, and people tested for gonorrhea since January receive this information so they can act upon it." People who have had a negative gonorrhea test since Jan. 11 may wish to ask their physician if they should be retested for gonorrhea.

Abbott notified its customers (clinical laboratories) to discontinue use of all test kits and to destroy any

(continued on page 94)

Preconception Issues in HIV

PAMELA J. DOLE, EDD, MPH, FNP, ACRN

Most women infected with HIV are of childbearing age and often choose to have children. Couples are concerned about transmitting HIV to unborn children or to their HIV-uninfected partner. What can be done to reduce HIV transmission?

Reducing HIV Transmission to the Unborn Child

Vertical or perinatal transmission refers to an HIV pregnant woman transferring the virus to her unborn child. Vertical transmission rates are 15–25 percent in industrialized countries like the United States for women not on antiretroviral therapy (ART).[1,2] HIV can also be transmitted antepartally (during pregnancy), intrapartally (during delivery), and postpartally through breast-feeding; most of all infections are thought to occur late in pregnancy (20%–33%) or during delivery (45%–80%); breast-feeding adds an additional 15–35 percent globally.[1,2] Reducing these risks requires the patient to plan for pregnancy with a multidisciplinary team that includes an HIV healthcare provider and an obstetrical specialist.

The AIDS Clinical Trials Group (ACTG) 076 study showed that perinatal HIV transmission could be reduced to 7.6 percent in women taking zidovudine (ZDV, AZT) by the third trimester of pregnancy and during delivery, and when the drug was administered immediately to newborns.[3] While monotherapy is no longer recommended for pregnant women, adding zidovudine (ZDV) to current regimens is the current recommendation of the Centers for Disease Control (2000). Single-dose nevirapine is currently being studied in HIVNET 012 or Pediatric ACTG 250/316/353 as an alternate to ZDV.[4,5] Combined ART therapy can further reduce the possibility of transmitting HIV to an unborn child to less than 2 percent.[6]

The Antiretroviral Pregnancy Registry tracks adverse effects of antiretroviral therapy (ART) to children who have been exposed to ARTs during pregnancy. (Information about the registry can be obtained by calling 800-258-4263 or online at: www.apregistry.com.) A 4-year follow-up of infants exposed to ZVD found no differences in lymphocyte subsets; in weight, height, and head circumference z scores; or in cognitive/developmental function versus infants who were not exposed to ZVD.[7] Several children had unexplained ophthalmic findings, and another child had asymptomatic cardiomyopathy. No deaths or malignancies had occurred at the time of follow-up.

The initiation and management of antiretroviral therapy are typically the same for both HIV-pregnant and HIV-nonpregnant women, except for the use of some contraindicated medications. Women who have not initiated ART and do not have an impending need to begin therapy (CD4+ counts >350 cells/mL or HIV-1 RNA levels <55,000 copies/mL) may wish to delay therapy until the second trimester when organ development is complete. Although the risks associated with ART use in pregnancy are rare, they include mitochondrial dysfunction (hepatic, hematologic, others), end-organ toxicities, development of ART resistance both to mother and child, and potential adverse maternal outcomes. While study data on the use of ART in pregnancy with and without the use of a protease inhibitor (PI) is often conflicting, some reported adverse maternal outcomes include preterm delivery, anemia, nausea and vomiting, aminotransferase elevation, and hyperglycemia.

ARTs contraindicated during pregnancy include efavirenz (Sustiva®, Bristol-Myers Squibb) and hydroxyurea; these drugs will need to be switched prior to conception because of possible birth defects. Indinavir (Crixivan®, Merck & Co.), d4T (Zerit®, Bristol-Myers Squibb), ddI (Videx®, Bristol-Myers Squibb), and amprenavir (Agenerase®, GlaxoSmithKline) should be used with caution and careful monitoring, as some late pregnancy toxicities have been noted.[8]

Beginning ART prior to conception allows for adjustment and treatment of side effects before possible pregnancy-related nausea. All women need to be on folic acid 0.4 µg daily prior to conception to avoid spina bifida and other neurological malformations in early pregnancy.

In addition to antiretroviral therapy, refraining from breastfeeding will also significantly reduce the possibility of transmitting HIV to the newborn child.

Women need to be counseled about cesarean section at delivery despite conflicting recommendations. Current studies have shown no difference in perinatal transmission rates between women on ART who had vaginal (5.5%) versus cesarean-section (4.5%) deliveries.[9] There is no evidence of cesarean section benefit if the women is already in labor or has ruptured membranes, so the procedure must be scheduled prior to 38–39 weeks of gestation. Cesarean section is only beneficial when the viral load is greater than 1000 copies/mL near term, even if the individual is on ART, or in women who are not on ART.[10] There are increased risks of morbidity with cesarean versus vaginal deliveries, especially with low CD4 lymphocyte cell counts.[11]

It should also be noted that pregnancy does not lower the mother's CD4 lymphocyte cells.[12]

Reducing HIV Transmission to an HIV-Uninfected Partner

Preconception counseling can significantly reduce HIV transmission for serodiscordant couples (one HIV-seronegative and one HIV-seropositive partner). However, preconception counseling is often omitted by healthcare professionals out of fear of medical legal repercussion should the HIV-uninfected partner seroconvert (become HIV-positive).[13,14] Failure to discuss risks associated with unsafe sex, or to provide guidance about how to reduce or minimize HIV transmission risks, may actually place discordant couples at an increased risk for unsafe behavior. HIV transmission risks should be discussed often with both individuals present and the discussion needs to be *documented in the medical record.* It is important to know your institution's policy on this topic.

The safest methods of conception are those that do not utilize intercourse. Options such as adoption, in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), or intrauterine insemination should be explored. However, while there is little or no HIV transmission with these methods, they have high economic burdens with variable coverage by third party payors.

If the woman is HIV-infected, consider intrauterine insemination or self-insemination to facilitate HIV risk reduction to her uninfected partner. This would include fertility timing and "turkey basting,"[15] an unconventional method of self-insemination utilizing a baster or syringe to insert semen into the vagina during ovulation. It is an affordable option for many patients and avoids sexual intercourse, thus keeping the uninfected partner safe.[16]

If the man is HIV-infected, the couple may want to consider sperm donation by an uninfected male to keep the uninfected partner safe. Alternatively, recent studies have shown sperm washing to be a promising alternative. There have been no HIV seroconversions from sperm washing when patients have been on ART, when semen viral loads (VL) are undetectable, and when CD4 lymphocyte cell counts are above 200.[13,14,17]

Preconception counseling for HIV-infected men should include education regarding the impact of ART on HIV concentrations in semen. HIV concentration in semen is twice as high as serum blood levels. Most men believe that an undetectable HIV serum blood level means that HIV is also undetectable in semen and thus they may abandon safer sex practices.[18] Studies have found that after 6 months of ART therapy, 15–34 percent of men have detectable seminal HIV VL, and after 18 months of ART, most men will have undetectable HIV semen viral loads; however, one study found that 2 men out of 7 continued to have detectable HIV in the semen after 2 years of ART treatment.[19,20]

If patients are not open to any of the aforementioned suggestions and choose to have unprotected sex, then the risk of transmitting HIV infection must be reiterated in the presence of both part-

(continued on page 95)

Bailey House: The Future Starts with a Place to Live

REGINA R. QUATTROCHI, ESQ, EXECUTIVE DIRECTOR, BAILEY HOUSE

Bailey House, formerly known as the AIDS Resource Center, was founded in 1983 by a group of clergy, West Village businesspeople, and gay and lesbian activists. They were witnessing friends and community members, devastated by what was then a new disease, become homeless and lose access to the care and resources they needed. The founders believed that housing is a fundamental human right and that no one is more vulnerable to the ravages of homelessness than people living with HIV/AIDS. They raised money to rent apartments for these newly homeless people and eventually were able to secure a building that became the first congregate living facility for people with AIDS in the nation.

The housing and services that Bailey House provided allowed many early residents to survive long enough to take advantage of the life-sustaining breakthroughs in medical therapies. Without stable housing and support, many of our clients would have died before these treatments became available.

Our housing programs have become the models that have ensured effective services for homeless people with HIV/AIDS throughout the country and around the world. Through our Technical Assistance Program Evaluation department (TAPE), Bailey House is able to share the expertise in housing and service development gained over the last 19 years with AIDS service agencies around the country.

Twenty-one years after the first cases of AIDS were seen in New York, homelessness among people with HIV/AIDS remains a crisis. Bailey House provides supportive housing to people with HIV/AIDS and their families through three programs: the Supportive Housing Apartment Program, which features 90 apartments throughout New York City for individuals and families; Bailey-Holt House, our 44-unit congregate living facility in Greenwich Village; and our newest program, Schafer Hall in East Harlem, which is geared to single parents and their children and to older adults, two groups of people who are more at risk for homelessness.

In addition to our housing programs, Bailey House operates the East Harlem Case Management program, which provides supportive services, including a food pantry and housing placement assistance, to clients who live in the community so they may stabilize their lives and improve their health.

Bailey House began offering vocational and educational services in 1995, when clients began experiencing what has been referred to as the "Lazarus Syndrome"—coming back to life after thinking—and feeling—like they were going to die. The INVEST NYC program offers literacy services, job readiness training, education, and job-placement services to 150 clients with advanced HIV or AIDS each year, many of whom face additional barriers to employment. Approximately 60 percent have a history of substance abuse, 19 percent have dealt with mental health issues, and 75 percent are ex-offenders.

In 1987, we began sharing our best practices for our successful models of housing and supportive services. The TAPE department offers support to AIDS service providers and HIV/AIDS services consumers to improve the availability and effectiveness of services for PWAs across the country. Through TAPE, Bailey House is able to further address the widespread need for permanent, affordable housing for PWAs and share its expertise in adapting service models to meet the unique needs of PWAs.

While the primary focus of TAPE's services is New York City, several programs offer training through collaborations with other agencies in other parts of the country such as AIDS Housing of Washington. The Technical Assistance (TA) Clearinghouse (www.taclearinghouse.org) is an Internet-based service that provides information useful to anyone working with HIV/AIDS programs who accesses the TA provider database, funding updates, and best practices pages as well as PWAs looking for training and services designed just for them. With over 2400 registered users and more than 1000 hits per month, the TA Clearinghouse serves clients at varying levels of organizational development and use of technical assistance—from those who simply need the definition of technical assistance to those who have worked with a variety of consultants and those who are searching for full-time employees through the job-posting database.

In addition to the TA Clearinghouse, agencies can access technical assistance through a variety of TAPE programs:

1. The Housing and Training Technical Assistance program works to disseminate resources on how to develop and manage supportive housing programs.
2. The Fiscal Infrastructure program uses training and one-to-one assistance to help nonprofit organizations stabilize their infrastructure and expand their capacity by acquiring effective fiscal management tools.
3. The Program Evaluation Services program works with organizations to create and follow outcomes-based evaluation models.
4. The AIDS Service Organizations Management Institute (ASOMI) provides a variety of technical-assistance resources, including fiscal infrastructure and management guidance, to AIDS organizations led by and serving people of color.
5. Through the Conflict Resolution Program, direct mediation services are available to organizations and individuals affected by HIV/AIDS who seek mediation for disagreements.

In the last year, we have trained over 1500 individuals from over 200 organizations and provided direct TA to 60 agencies. The TAPE department has assisted in the creation of more than 3700 AIDS housing units in New York City, and reaches approximately 3000 clients per year.

The future for Bailey House includes offering technical assistance to AIDS service organizations in South Africa, expanding our INVEST job-readiness program to include intensive computer training and more connections with local industry, and special housing assistance, education, job placement, and other services for formerly incarcerated PWAs. Further information on Bailey House can be found on our website at www.bailey-house.org.

Regina R Quattrochi, Esq, has served as Bailey House's Executive Director since 1991. Prior to joining the staff, she served on the Board of Directors for five years.

dear bailey House,
Thank you for giving me and my mom a place to live! The people here are nice and help us a lot. Mom helps me with my homework and goes to school too.
THANK YOU!
Love, Elena

For nearly 20 years, Bailey House has demonstrated that "The Future Starts with a Place to Live." Housing is a vital resource to our clients who, before coming to Bailey House, could not effectively care for their health. We provide Elena and her mother and hundreds of other homeless people with AIDS a safe, secure home. We also provide the support they need to adhere to complex treatment regimens while helping them develop independent living skills and regain control of their lives. Hundreds of other clients with HIV/AIDS take part in our basic education and job readiness and job placement programs.

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The future starts with a place to live

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HIV and Hepatitis in Prisons and Jails: the Hidden Epidemic

ELIZABETH HERBERT, MANAGING EDITOR, *HIV & HEPATITIS EDUCATION PRISON PROJECT REPORT*

By now we're familiar with the numbers: 42 million people living with HIV/AIDS worldwide; AIDS deaths in 2002 surpassing 3 million across the globe. In their recent biannual report, UNAIDS and the World Health Organization released these and other statistics, noting the shift of the HIV epidemic toward women, as well as the crisis the epidemic is causing in Africa, China, India, and other Asian nations.

What is not as well publicized—but just as much a public health crisis—is the prevalence of HIV/AIDS and hepatitis in US prisons and jails. The overall rate of confirmed AIDS cases among the nation's prison population is four times the rate in the US general population, according to a report released in October 2002 by the Bureau of Justice Statistics. Just in state prisons alone (not counting federal prisons or community jails), 2.2 percent of male inmates and 3.6 percent of all female inmates were known to be HIV-positive.[1] That means that 52 of every 10,000 prison inmates had confirmed AIDS, compared to 13 out of 10,000 in the rest of the US population.

Hepatitis C infection is also an emerging public health crisis, particularly within incarcerated communities. Surpassing HIV, hepatitis C (HCV) is now the most common blood-borne infection in the US, with an estimated 4 million infected.[2,3] A great number of those affected by hepatitis C—approximately 30 percent—served time in a correctional facility. According to a report to Congress by the National Institute of Justice and the National Commission on Correctional Health Care (NCCHC), the 17 percent to 18 percent prevalence of HCV among inmates (which they note is probably an underestimate) is 9 to 10 times higher than the prevalence in the nation's population as a whole.[4]

Because jails and prisons have such large and concentrated populations with HIV/AIDS or hepatitis (or populations at high risk for both diseases), the settings offer a unique opportunity to reach a population that is largely underserved and difficult to identify and treat in the general community. Inmates who are released untreated are likely to transmit their disease to others in their communities and will create a larger financial burden on the public health system as their disease, left untreated, worsens.

But while prisons and jails would seem to be an effective place to screen, treat, and educate inmates, healthcare services (including intake screening, treatment, education, and community outreach services) vary widely from prison to prison. With some notable exceptions, correctional HIV care has often lagged behind the usual standard of care.

HEPP Report began as the combined effort of Drs. Anne De Groot and Rick Altice, who were soon joined by Joe Bick, David Thomas, David Paar, and several other leaders in the field of correctional medicine. The mission: to reach HIV-care providers in corrections and provide them with up-to-date HIV-treatment information. HIV care provided by correctional physicians impacts a major proportion of HIV-infected individuals in this country—17 percent of the total number of people with HIV/AIDS in the US, according to the NCCCH report.

With this goal in mind, the first issue of *HEPP (HIV and Hepatitis Prison Project)* was faxed to 1200 correctional healthcare providers in 1998. Five years later, the *HEPP Report* reaches nearly 20,000 correctional physicians, nurses, and administrators each month by e-mail, fax, and mail. Since many correctional physicians do not have Internet access within the prison (standard policy for many correctional facilities), and are prohibited from participating in off-site CME events sponsored by the pharmaceutical industry due to their status as state or federal employees, faxing was the most effective way to reach them directly.

The *HEPP* editorial and advisory board comprises leaders in correctional healthcare, including specialists in HIV, hepatitis, tuberculosis (TB), and other infectious diseases. While *HEPP* began with a focus on HIV/AIDS care in prisons and jails, it expanded in 2000 to cover hepatitis, TB, and other infectious diseases with a high prevalence in correctional populations. Each month, *HEPP* provides correctional healthcare providers with relevant information on managing HIV/AIDS, hepatitis, and other infectious diseases, including new drug information, case studies, algorithms, news briefs, and conference updates. Each issue of *HEPP* also provides CME credit through the Brown University CME program.

While the *HEPP Report* brings the latest news in immunology and virology to its readers, it does so with an eye to how this information can best be applied in the correctional setting—it tries to provide "how-to" information for the correctional doctors and nurses it reaches. As always, it seeks to elevate the standard of care for prisoners infected with HIV/AIDS, hepatitis, and other infectious diseases, and to promote a level of care in prisons and jails equivalent to the community standard. *HEPP* also encourages providers to improve their networks with correctional, academic, or community-based experts in the field of HIV, hepatitis, and TB.

When we look at the progress made over the last several years in HIV/AIDS correctional care, we are heartened. Care provided to HIV-positive inmates has improved—HAART therapy is now the treatment norm; most inmates can request an HIV test if they are unaware of their status; and more and more correctional facilities have adopted HIV/AIDS treatment protocols and programs.

However, there is still a long way to go. Only a few states universally provide screening for HIV and hepatitis upon intake; even if inmates are tested, not all are guaranteed to receive their results. There is no nationally recommended (or enforced) standard of care for HCV infection in state prisons, and, among inmates who are diagnosed with HCV, treatment is selective and not universal. Often, people cycle so quickly through prison and jail (particularly jails, where individuals may remain for less than 48 hours), that testing, counseling, and the initiation of treatment remain daunting logistical hurdles.

As front-line providers for so many of the nation's HIV and hepatitis patients, correctional physicians have the opportunity to reach a significant portion of this country's infected population who might not otherwise have access to or choose to take advantage of reliable health care. Inmates at all correctional facilities should have the option to be tested, to receive quick and confidential reports on those tests, and to receive treatment and counseling. The NCCHC report to Congress recommends routine screening, testing, and education for all inmates, noting that it would be both cost-effective and of enormous benefit to the public health of our nation. At *HEPP*, we back this recommendation and are committed to continuing to provide correctional healthcare workers with the tools to do so.

For more information, visit the *HEPP Report* online at www.hivcorrections.org.

Elizabeth Herbert is the Managing Editor of the HEPP Report *at Brown University, Providence, RI. Website: www.hivcorrections.org.*

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Infectious Disease In Corrections

Prison Health is Public Health

According to a recent report to congress, 20 to 26% of all people living with HIV in the United States, 29% to 43% of all those infected with the HEPATITIS C virus, and 40% of all those who had tuberculosis disease in 1997 passed through a correctional facility that year.

For many inmates, correctional facilities offer the first opportunity for consistent health care. This makes jails and prisons good places to provide infectious disease testing, treatment, and education.

About HEPP Report

HEPP Report, a forum for correctional problem solving, targets correctional administrators and HIV/AIDS and hepatitis care providers including physicians, nurses, outreach workers, and case managers.

Published monthly and distributed by email and fax, HEPP Report provides up-to-the moment information on HIV/AIDS, HEPATITIS, and other infectious diseases treatment, efficient approaches to administering treatment in the correctional setting, national and international news related to infectious diseases in prisons and jails, and changes in correctional care that impact HIV treatment.

Each issue also provides CME credit through the Brown University Office of Continuing Medical Education.

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Birds, Bees and Bugs: Fostering HIV Prevention and Self-Respect in LGBTQ Youth

DAVID EDISON, FOR THE HETRICK-MARTIN INSTITUTE

Perched on a far corner of downtown Manhattan's Astor Place, the Hetrick–Martin Institute (HMI) leads a 24-year mission to rescue lesbian, gay, bisexual, transgender, and questioning (LGBTQ) youth from the array of dangers they face daily. Through solo and family counseling, case management, youth leadership, and education, the dedicated staff of HMI work tirelessly to help ensure the future of hundreds of youth each year. In addition to their drop-in center, HMI is also home to the Harvey Milk School, the first and largest accredited public school in the world to address the specific needs of LGBTQ youth. Whether it be at school, at home, or on the streets, HMI strives to provide a safe environment in which LGBTQ youth can achieve their full potential. That mission, of course, would hardly be complete without seriously addressing the issues of HIV and self-protection.

"HIV prevention is fundamentally integrated into the mission of the agency, which is our commitment to LGBTQ youth," explains Executive Director David K. Mensah. "That means we are interested in their overall health and well-being, their past, present, and future. If you look at all the specific activities or interventions that we pursue with LGBTQ youth, you see that there is a consistent HIV prevention strain throughout—HIV is such a significant social and public health issue right now that it gets a headline in every group."

LGBTQ youth face very specific risks when it comes to exposure to HIV. "They don't really get the option to grow up the same way everybody else does. You may know you're attracted to somebody from a very young age, but if that attraction isn't socially acceptable, then you can't tease, flirt, be chided, play games, or engage in any of the usual overt and totally safe experimentation that fosters gender and sexual identity. The older you get, the worse it gets, because you have full knowledge of how unacceptable those behaviors would be. So your exploration, when it occurs, becomes forced or concentrated into these isolated, shame-based events that have much more urgency and intensity, [and] that makes you more likely to make bad choices or be abused."

HMI targets the issue of HIV in ways both oblique and direct. "Within a counseling setting, a youth might disclose that he is nervous because he may have had unprotected sex, that he's terrified and unsure what to do. While talking about what happened, about what's going on with him in general that might have led to this, a significant goal would be for him to get a baseline HIV test—and agree to get retested at three months and six months out. The idea is to combine emotional support-based prevention with realistic, immediate action."

A less direct method of prevention might occur in HMIs after-school program, during any one of a broad variety of youth development groups. "We may have a group that includes nutrition, public health, substance abuse, and within that group there will be a specific curriculum that talks about safer sex, condom use, and the risks of various behaviors. We also help the youth understand the issues particular to being LGBTQ—including issues of gender and sexuality.

"In almost all of our social and emotional groups, we spend time talking about identity development. This plays out in all the groups, but it emerges very strongly in groups that use art as a vehicle. It's so much easier to talk about what your picture means to you instead of talking about yourself. One of the reasons HMI was founded was that nobody believed gay youth existed—they were horrifically isolated. We bring them together to talk about issues, gently challenge negative norms, and allow them to develop positive self-images. A lot of what we do is simply honor people's choices about themselves and their self-expressions."

HMI tries to address HIV prevention in ways that may seem indirect, but Mensah quickly points out how crucial these holistic efforts can be. "We believe it's hard for people to take care of their bodies if they secretly hate them. We focus on some simple things like developing a relationship with a healthcare provider. To do that, you don't have to love everything about yourself—but you have to value yourself enough to care.

"We do constant outreaches to both the community at large and the youth who find us daily at our drop-in center. We spread basic safer-sex messages; we try to ensure that they have access to condoms—anything that allows youth to protect themselves on an immediate basis. We have a van that goes out once or twice a week with both outreach staff and student interns, targeting locations we know LGBTQ youth frequent. Our outreach staff are also our case management staff and they interact closely with youth who visit—youth may come here and eat for a week, and when they decide they're ready to get some services, they find out the person who's been sitting across from them this whole time is also their case manager."

Even within the LGBTQ community, subdivisions exist that present unique challenges in regard to HIV prevention. "We have a high concentration of transgender youth here—some of whom want to get hormones on the streets. One of the first things we heard from the medical community is that the youth are getting injectable hormones, which they believe to be stronger and quicker. Of course, we immediately recognized the need to talk about this with our youth—when you add a syringe to the equation, the exposure issues skyrocket.

"While we neither condemn nor encourage their behavior, our purpose is to educate them about the consequences of their choices. We take a fairly clear line about drug use, for instance, that is not so much oriented around the condemnation of drugs, as it is around consequences—how drugs may limit and affect your choices, particularly about sex.

"We combine the development of self-esteem, of looking forward to your own future, and the practical side of HIV and sex education, which is how to actually take care of yourself." Mensah refers again to two key directives of HMI: safety and achievement of full potential. "While we feel like we're at the point where we can assume the former—it is physically safe here—we also need to remember that every day we need to find ways for youth to keep *themselves* safe. So we need to spend time recognizing them as mature, capable, and responsible. If we don't enter this as partners, we destroy the very thing we need most to ensure their safety. We don't tell stories to scare them and we don't lie—we create engaging dialogue with those who can talk, and we find other vehicles for those who prefer not to use words."

To achieve its directives, the Hetrick–Martin Institute combines specific, prevention-based HIV education with the novel idea of generating considerate and self-respecting young people who want to protect themselves—and are well-equipped to do so. HMI has been helping LGBTQ youth along their way for nearly a quarter of a century, and their multi-pronged approach to HIV prevention reflects what they've learned: "How do you talk with people whom you value and respect? You tell them the truth."

David Edison is a graduate of Brown University who lives in New York City. He is a freelance writer and editor, specializing in gay and lesbian issues. N

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To learn more or to make a donation, visit our website: www.HMI.org

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Senior Action in a Gay Environment

ELIZABETH KLING, FOR SAGE

People over age 50 with HIV/AIDS have relatively few resources targeted to their specific emotional and physical health needs. For this reason, Senior Action in a Gay Environment (SAGE), a New York City-based social service and advocacy organization serving senior LGBT (lesbian/gay/bisexual and transgender) communities, provides a much-needed service—a program called SAGE Positive. Offering case management, benefits counseling, mental health services, friendly visitors, and support groups, this program provides significant assistance to an extremely isolated subsection of the HIV-positive community.

Ageist attitudes in both the mainstream and LGBT communities play at least some part in explaining why most HIV/AIDS services have been designed exclusively to assist younger people. But older LGBTs with HIV/AIDS have unique needs that must be addressed. Medications prescribed to treat diseases associated with aging often conflict with AIDS treatment regimens, and providers must be aware of these drug interactions, as well as the physical, emotional, and social changes that often accompany aging.

Older LGBTs with HIV/AIDS often feel uncomfortable discussing their issues with individuals in their 20s, 30s, and 40s, who make up the bulk of AIDS support groups in New York City. Yet, older LGBTs have a particularly strong need for the encouragement and support offered by these groups. The stigma of aging, combined with the challenges of identifying as LGBT, causes many to lead isolated lives, as the LGBT community tends to overlook its members once they reach a certain age. Being HIV-positive often compounds this isolation, causing many to discontinue dating and lose contact with friends who don't share their HIV-positive status.

SAGE Positive support groups, moderated by professional social workers, provide these individuals with a safe and comfortable environment to discuss the particular challenges of growing old with HIV/AIDS. They are a source of connection and an avenue for the development of informal social networks outside the groups. Members exchange telephone numbers, check in with one another between meetings, and make hospital visits. SAGE Positive is currently assisting clients ranging in age from 50 to 80 and has been in operation since 1989.

In addition to serving HIV-positive LGBTs over age 50, SAGE has a broader mandate to provide social services, educational programs, and recreational activities to the growing senior LGBT population, which numbers 75,000 strong in New York City. SAGE also works on a national level, advocating for the rights of senior LGBT people, operating as a clearinghouse of information on LGBT aging, and fostering a greater understanding of LGBT aging issues in the mainstream culture, particularly among service providers who work in mainstream institutions.

SAGE's work is especially crucial considering that LGBT seniors remain five times less likely than the general older population to access mainstream services such as senior centers, housing assistance, meal programs, Food Stamps, and other entitlements. Many came of age during a period of intense hostility and prejudice against homosexuality, and a legacy of harsh discrimination leaves them wary of mainstream institutions. Compounding the need for SAGE services is the fact that LGBT seniors often lack traditional sources of support for the elderly—spouses and children. Many LGBT seniors live in secrecy and isolation, with their basic needs unacknowledged and unmet.

To fill this gap in services, SAGE steps in with crisis intervention, counseling, case management, benefits assistance, friendly visiting, and referral to community resources. Professionally led support groups help clients deal with issues of bereavement, coming out, progressive illness, and Parkinson's disease, among others. And through its community organizing work, SAGE connects members within their own neighborhoods, creating a network of individuals sharing social and recreational activities and providing assistance to one another in times of illness and infirmity. To enhance quality of life, SAGE offers over 100 recreational and educational activities per month, from yoga, painting, opera appreciation, and rap groups to a daily senior "drop-in" center. All recreational groups are run by knowledgeable volunteers trained by SAGE staff in group facilitation skills.

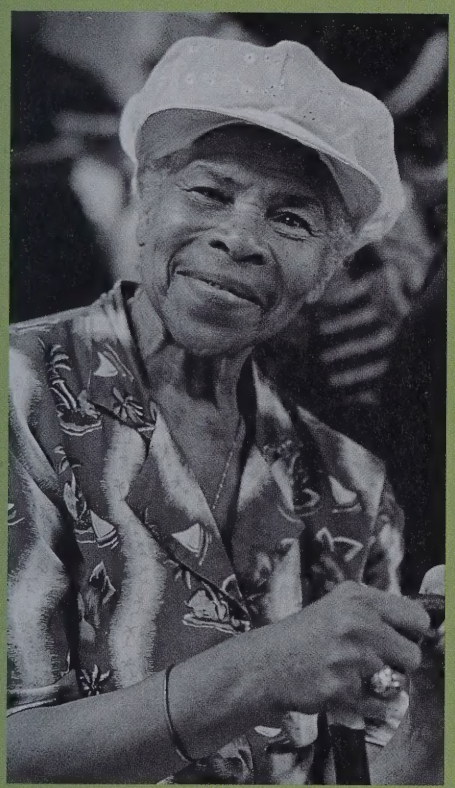
Recognizing that the combined effects of ageism and homophobia are robbing LGBT elders across the country of vitality in their old age, SAGE is currently launching several national initiatives aimed at insuring a better aging future for all LGBTs. One such endeavor is the development of the first "LGBT Sensitivity and Cultural Change Training Guide," designed for nursing homes, assisted living facilities, and other long-term care providers. This guide will provide institutions with the means to inform and sensitize their staff to the needs of their diverse LGBT residents. Through another initiative, SAGE is answering the call among LGBT elder advocates for more information by conducting a National Needs Assessment and Technical Assistance Audit. With the data gleaned from this survey, SAGE can more accurately evaluate the current level of services available for the LGBT elder population nationwide. SAGE can then use this information to help outline the future direction for the LGBT aging movement in policy and program development.

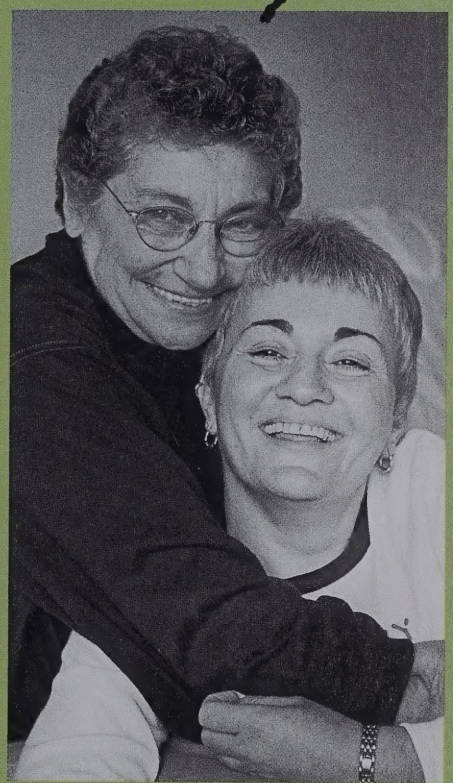
Founded in 1977 as the nation's first social service agency for gay elders, SAGE is the oldest and largest senior LGBT organization in the US. Through SAGENet affiliates across the country, the work of serving, advocating for, and improving the lives of LGBT elders is expanding into increasingly remote areas. And with SAGE's growing education and advocacy efforts, LGBT elder issues are becoming a part of the national agenda on aging.

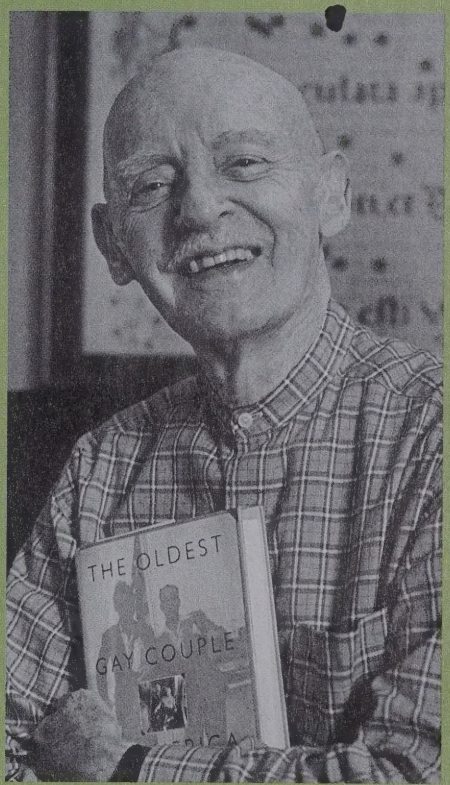
For more information please visit www.sageusa.org.

Elizabeth Kling, MA, is a SAGE volunteer who writes on aging issues in the lesbian, gay, bisexual, and transgender communities. N

It's not how old, it's how well!







Being gay isn't just about being young. It's about a lifetime of community, and the freedom to be who we are. SAGE is the nation's premier social service and advocacy organization for lesbian, gay, bisexual and transgender seniors. We're a force against ageism ... a place to turn when you're in trouble ... and a dynamic source of social and enrichment opportunities for all. We welcome your participation and support.

A Special Message to Readers of NUMEDX:

Today in New York City, over 12% of HIV/AIDS cases involve people over the age of fifty. Yet most services neglect this population. SAGE Positive is a pioneer program addressing the unique needs of LGBT individuals over 50 who are living with HIV. SAGE Positive clients have access to a full range of social services. For more information, call SAGE or visit us at www.sageusa.org.

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Services and Advocacy for GLBT Elders

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Photographs by Penny Coleman

What's So Funny About AIDS?

KAREN OCAMB

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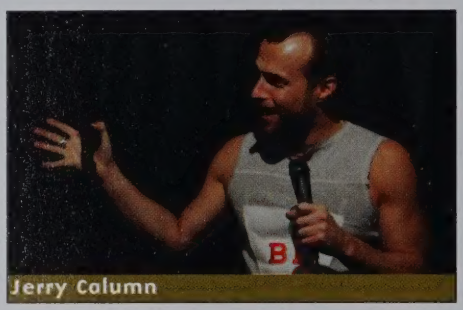
"The environment I operate in is often antigay and anti-HIV, and...what I do when I'm up there is more than tell jokes. I educate and I open people to new perspectives," says Calumn, whose day job is as the executive director of the nonprofit American Academy of HIV Medicine (AAHIVM), an independent group that administers a national credentialing program for HIV specialists. "I purposefully dress in more revealing clothes so people think of me as available. Then—wham—I hit them with the fact that I am positive. After the second or third time I did it, I overheard two women saying later, 'Wow. He is so cute. I would have never thought he was positive.' That is the punch for me. That's the education. I don't always get a laugh. But I don't need to. At times telling AIDS jokes is challenging. But we've got to have a sense of humor about it. It helps relieve the tension and people can hopefully grow from it."

The long hall entrance to The Belly Room is lined with photos of now famous comedians—Whoopi Goldberg, Arsenio Hall, Roseanne— who played the Comedy Store on the Sunset Strip when they were young and outrageous. In the early 1990s, owner Mitzi Shore opened the intimate back room for a "Gay Night," seen by the gay community as an important historical overture after years of homophobia by comics such as Sam Kinison and Andrew "Dice" Clay. Though not called the "Gay Night," Sundays in The Belly Room are reserved for openly gay Adam Barhardt's "Comedy Revival" which features gay and straight comedians and audiences, some apparently tickled by the crude, rude, and graphic.

Calumn, who's been positive since 1994, doesn't just blurt out his status. He warms to it by talking about how, at 36, he's "clearing the bench on the dating scene." One of the challenges to dating, he tells a friendly audience, is that "I am an HIV-positive person. I run a national HIV organization. That's always a challenge—you're never quite sure how people are going to respond when you reveal that. Obviously, this group got quiet." The crowd, including nervous heterosexual couples, breaks into laughter.

Calumn spins a tale about his HIV lecture trips to rural Texas, where the men announce they're carrying guns and where the society ladies (who apparently believe "the higher your hair, the closer you are to Jesus") ask him, "How does it really feel to be dying?" Given their smoking habits, he tells them, "I think your reservation will be up before mine." But the biggest laugh comes when Calumn talks about the publicity and controversy surrounding the new HIV-positive Sesame Street character. "Do you know what it feels like to work 15 years in an industry and get upstaged by a Muppet?"

"One has to find humor in it," Calumn says. "And there's also a physiological response with laughter—there's an immediate release of helpful hormones that fight depression and have other healthful effects. That's one thing that keeps me


Jerry Calumn

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Author and *Saturday Review* editor Norman Cousins opened up a new field in mind–body study with his seminal book *Anatomy of an Illness.* Cousins wrote about how high doses of vitamin C and lots of laughter helped heal his degenerative ankylosing spondylitis. The Cousins Center for Psychoneuroimmunology at the University of California at Los Angeles (UCLA) continues what the center describes as studies across the disciplines of neuroscience, integrative physiology, behavioral biology, immunology, psychiatry, psychology, and clinical medicine, including its effects on HIV/AIDS.

Donny Moss, another openly gay stand-up comedian, is also involved with the HIV/AIDS community as the HIV and Hepatitis C liaison for the Roche pharmaceutical company. "I walk a fine line because I help facilitate communication between the community and the company to make sure the community's voice is represented in the work we do and to make sure we do what's right," says Moss. "I'm also Roche's voice within the community."

Moss, 30, was prompted to try his turn at stand-up by responses to his personal ad on a gay website. "People kept asking if I was a stand-up comedian because all the answers about myself were so over the top. There's also a picture of me hugging a chimp with the caption, 'Me and my last boyfriend from Planet Out.' I just thought, with all these people asking me if I am a comedian—there's probably something there," Moss says. For his first gigs, he went to comedy venues in New York City, where newcomers can get five minutes of stage time if they bring five to ten customers. He now performs every Friday and Saturday night at the Boston Club in Greenwich Village before mostly heterosexual audiences.

"Gay crowds are tougher," he says. "They have very high expectations," at least in Manhattan.

"I like to talk about mundane topics everyone can relate to—but from a gay perspective. And then I wait a beat and catch them off-guard. I like the shock value. For instance, here's a short joke: My parents bought me a cute dog for my birthday and it turned out to be a chick magnet—so I had to put it to sleep," Moss says, adding that he's really a dog lover.

Like Calumn, Moss acknowledges the environment for stand-up can be filled with "jokes" about racism, sexism, and just about anything sexual. "When you have a drunk, rowdy crowd, they just want to hear filth. And the comedians give it to them. But that kind of humor is just tacky. They're never going to make it on Letterman," Moss says. "I like to shock—but not about AIDS. I can't imagine using AIDS as a way to get a laugh—especially in a five- to ten-minute set. There are three subjects I won't do: cancer, AIDS, and the World Trade Center. Others do joke and people laugh nervously, at best."

Moss cites, as an example, a heterosexual woman who complained about never having sex. She'd go to her gynecologist and get tested for STDs and "joked" about how she'd at least like the chance to worry about getting AIDS. "I was offended," Moss says. "I thought she was using AIDS in an irresponsible way. I don't know why she had to bring AIDS into a joke like that."

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However, Moss, who is HIV-negative, concedes, "Talking about HIV may be more appropriate when coming from someone who has it. It's less offensive."

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Pull-Out Drug Adherence Chart

DAILY DOSING OF ANTIRETROVIRAL AGENTS

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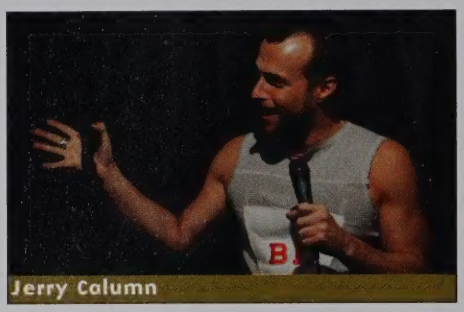
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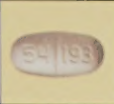
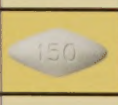
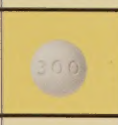
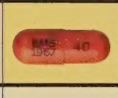
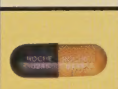
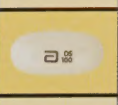
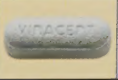
DAILY DOSING OF ANTIRETROVIRAL AGENTS

(DRUGS ARE LISTED ALPHABETICALLY, WITHIN EACH DRUG CLASS)

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS		STANDARD DAILY DOSING	ALTERNATE DAILY DOSING	POTENTIAL SIDE EFFECTS/OTHER CONSIDERATION(S)
Rescriptor® (delavirdine mesylate) Agouron Pharmaceuticals		4 x 100 mg tablets 3 times a day or 2 x 200 mg tablets 3 times a day		Rash; headache; fatigue; stomach upset; elevated liver enzymes. Should be taken at least 1 hour before and after didanosine and antacids. Should not be taken with St. John's Wort and many cardiac medications. Please see full prescribing information for the list of contraindicated drugs. PATIENT SUPPORT: WWW.PFIZER.COM/HML/HML.HTML | 888.777.6637
Sustiva® (efavirenz) Bristol-Myers Squibb		1 x 600 mg tablet Once a day	3 x 200 mg capsules once a day.	Rash, drowsiness, confusion, inability to concentrate, dizziness, vivid dreams, nausea, stomach discomfort, fever, insomnia, elevated liver enzymes. It is recommended that Sustiva be taken on an empty stomach, preferably at bedtime. Increased Sustiva concentrations are seen when this drug is taken with food, which may lead to increase in frequency of adverse events. Dosing at bedtime may improve the tolerability of nervous system symptoms. Women taking this drug should not get pregnant. This recommendation is based on studies which showed congenital malformations in monkeys given this drug; there are no human data available. PATIENT SUPPORT: WWW.SUSTIVA.COM | 800.334.4486
Viramune® (nevirapine) Boehringer Ingelheim		1 x 200 mg tablet 2 times a day		Rash; stomach upset; headaches; increased liver function tests. More rarely: hepatitis. Lead-in dosing lessens frequency of rash. For first 14 days: 1 x 200 mg tablet once a day while observing for rash. If no rash develops, dose increased to 1 x 200 mg tablet twice a day. PATIENT SUPPORT: WWW.VIRAMUNE.COM | 800.556.8317
NUCLEOSIDE ANALOGUES		**STANDARD DAILY DOSING**	**ALTERNATE DAILY DOSING**	**POTENTIAL SIDE EFFECTS/OTHER CONSIDERATION(S)**
Combivir™ (lamivudine/zidovudine) GlaxoSmithKline		1 x 150 mg lamivudine/ 300 mg zidovudine tablet 2 times a day		Nausea; loss of appetite; headache; fatigue; stomach discomfort (lactic acidosis). More rarely: Muscle wasting; anemia (low red blood cell count); neutropenia (low white blood cell count). Fixed combinations should not be prescribed for patients requiring dose adjustments. Should not be taken with Zerit. Retrovir should not be administered with either Combivir or Trizivir since these agents contain Retrovir as part of their combination formulation. | PATIENT SUPPORT: WWW.COMBIVIR.COM | 888.825.5249
Epivir® (lamivudine–also known as 3TC) GlaxoSmithKline		1 x 300 mg tablet once daily	1 x 150 mg tablet 2 times a day	Nausea. PATIENT SUPPORT: WWW.TREATHIV.COM | 800.722.9294
Hivid® (zalcitabine–also known as ddC) Roche Pharmaceuticals		1 x 0.75 mg tablet every 8 hours		Numbness, tingling, or pain in the hands or feet (peripheral neuropathy, seen in 17%–31% of patients); nausea; mouth ulcers. Should not be used concomitantly with didanosine. Do not take simultaneously with magnesium/aluminum-containing antacids. | PATIENT SUPPORT: WWW. ROCHEUSA.COM | 800.282.7780
Retrovir® (zidovudine– also known as ZDV or AZT) GlaxoSmithKline		1 x 300 mg tablet 2 times a day	2 x 100 mg tablets 3 times a day	Taking with food may minimize stomach discomfort. Nausea; stomach discomfort; headache; insomnia. More rarely: muscle wasting; anemia (low red blood cell count); neutropenia (low white blood cell count). Retrovir should not be administered with either Combivir or Trizivir since these agents contain Retrovir as part of their combination formulation. | PATIENT SUPPORT: WWW.TREATHIV.COM | 800.722.9294
Trizivir™ (triple nucleoside–also known as TRZ) combination AZT/3TC/abacavir GlaxoSmithKline		1 tablet 2 times a day AZT–300 mg 3TC–150 mg abacavir–300 mg		"Strong warning" due to a side effect of abacavir component with up to 5% of patients having a "severe, possibly fatal if untreated, allergic reaction." Area under the curve (AUC) similar to combivir + abacavir in a descriptive study. Careful patient selection for triple nucleoside combination important. Similar side effects to Retrovir (AZT), Epivir (3TC), and Ziagen (abacavir). Do not take if you had an allergic reaction to abacavir. PATIENT SUPPORT: WWW.TREATHIV.COM | 800.722.9294
Videx® EC enteric coated (didanosine–also known as ddI) Bristol-Myers Squibb		>60 kg 400 mg once daily and <60 kg 250 mg once daily	2 x 200 mg capsules Once a day	Numbness, tingling, or pain in the hands or feet (peripheral neuropathy, seen in about 15% of patients); nausea; diarrhea; headache; vomiting; rash. More rarely: pancreatitis. Alcohol may exacerbate toxicity. Avoid aluminum-containing antacids. Preferred formulation for once daily dosing. Take on empty stomach; swallow capsule whole. PATIENT SUPPORT: WWW.BMSVIROLOGY.COM | 800.272.4878
Videx® tablets (didanosine–also known as ddI) Bristol-Myers Squibb		2 x 100 mg tablets 2 times a day		Numbness, tingling, or pain in the hands or feet (peripheral neuropathy, seen in about 15% of patients); nausea; diarrhea; headache; vomiting; rash. More rarely: pancreatitis. Alcohol may exacerbate toxicity. Avoid aluminum-containing antacids. Take on an empty stomach 30 minutes before or 2 hours after a meal. PATIENT SUPPORT: WWW.BMSVIROLOGY.COM | 800.272.4878
Zerit® (stavudine–also known as d4T) Bristol-Myers Squibb		Patients >60 kg: 1 x 40 mg capsule, every 12 hours Patients <60 kg: 1 x 30 mg capsule, every 12 hours		Nausea; numbness, tingling, or pain in the hands or feet (peripheral neuropathy). Should not be taken with AZT. PATIENT SUPPORT: WWW.BMSVIROLOGY.COM | 800.272.4878
Zerit® XR (stavudine–also known as d4T) Bristol-Myers Squibb		Patients >60 kg 1 x 100 mg once daily Patients <60 kg 1 x 75 mg once daily		No food requirements or restrictions are necessary with Zerit® XR. Side effects, such as slight headache or abdominal pain, are generally mild. PATIENT SUPPORT: WWW.BMSVIROLOGY.COM | 800.272.4878
Ziagen™ (abacavir sulfate) GlaxoSmithKline		1 x 300 mg tablet 2 times a day		Nausea; vomiting; diarrhea; loss of appetite; insomnia. Serious allergic reactions have been reported in about 3%–5% of patients. The signs and symptoms of this reaction include fever, malaise, severe nausea, diarrhea, abdominal pain, sore throat, cough, shortness of breath, and rash. If allergic reaction is diagnosed, therapy should be discontinued and NOT restarted. Symptoms of allergic reactions usually appear within 6 weeks of starting therapy and resolve within 24–48 hours of stopping the drug. A rash without other signs of allergic reaction has also been reported in about 7% of patients. These rashes can usually be managed without stopping therapy. Patients experiencing hypersensitivity reaction (up to 5%) should discontinue the drug and not restart it due to potential life-threatening reactions. PATIENT SUPPORT: WWW.ZIAGEN.COM | 800.722.9294
PROTEASE INHIBITORS		**STANDARD DAILY DOSING**	**ALTERNATE DAILY DOSING**	**POTENTIAL SIDE EFFECTS/OTHER CONSIDERATION(S)**
Agenerase™ (amprenavir) GlaxoSmithKline		8 x 150 mg capsules twice a day	8 x 150 mg amprenavir with 2 x 100 mg ritonavir once daily or 4 x 150 mg amprenavir with 1 x 100 mg ritonavir twice daily.	Rash (seen in 20% of patients); diarrhea; nausea; vomiting; oral tingling and numbness. High fat meals should be avoided. Should be taken at least 1 hour before or after didanosine and antacids. Vitamin E supplements should not be taken with amprenavir. For usage with Methadone and/or oral (hormonal) contraceptives see http://www.fda.gov/cder/foi/label/2002/21007s11,21039s10lbl.pdf PATIENT SUPPORT: WWW.TREATHIV.COM | 800.722.9294
Crixivan® (indinavir) Merck & Co.		2 x 400 mg capsules every 8 hours	2 x 400 mg capsules of Crixivan with 2 x 100 mg soft gelatin capsules of Norvir 2 times a day; 1 x 400 mg capsules of Crixivan with 4 x 100 mg soft gelatin capsules of Norvir 2 times a day	Kidney stones (seen in 6%–8% of patients); nausea; vomiting; diarrhea; stomach discomfort; headache; insomnia; rash; back pain. Take on empty stomach 1 hour before or 2 hours after a meal. Drink at least 8 glasses of water daily. PATIENT SUPPORT: WWW.CRIXIVAN.COM | 800.850.3430
Fortovase® (saquinavir) Roche Pharmaceuticals		6 x 200 mg soft gelatin capsules 3 times a day	5 x 200 mg Fortovase with 1 x 100 mg ritonavir twice daily or 8 x 200 mg Fortovase with 1 x 100 mg ritonavir once daily or 5 x 200 mg Fortovase with 3 lopinavir/ritonavir (Kaletra) twice daily.	Nausea; diarrhea; stomach discomfort; insomnia; headache; increased liver enzyme levels. Take within 2 hours after a full meal. Saquinavir taken without food may have less bioavailability. PATIENT SUPPORT: WWW.FORTOVASE.COM | 800.910.4687
Invirase® (saquinavir mesylate–gel caps) Roche Pharmaceuticals		3 x 200 mg capsules 3 times a day Boosted dose with ritinovir highly recommended. See alternative dosing box.	5 x 200 mg Invirase with 1 x 100 mg ritonavir twice daily or 8 x 200 mg Invirase with 1 x 100 mg ritonavir once daily or 5 x 200 mg Invirase with 3 lopinavir/ ritonavir (Kaletra) twice daily.	Diarrhea, abdominal discomfort and nausea. Take 2 hours after a full meal. Do not take with grapefruit juice. Do not take with astemizole (Hismanal), terfenadine (Seldane), ergotamine (Cafergot), D.H.E. 45 or midazolam (Versed), or triazolam (Halcion). PATIENT SUPPORT: WWW.ROCHEUSA.COM | 800.910.4687
Kaletra™ (lopinavir/ritonavir) Abbott Laboratories		3 x 133 mg lopinavir/ 33 mg ritonavir capsules 2 times a day		Second generation protease inhibitor. Combines lopinavir (133.3 mg) and Ritonavir (33.3 mg). Same drug interactions and side effects as with ritonavir. During clinical trials, side effects reported were diarrhea of mild to moderate severity (14%–24%), nausea/vomiting (2%–15%/1.6%–5%), and abnormal stools (1%–6%). PATIENT SUPPORT: WWW.KALETRA.COM | 800.222.6885
Norvir® (ritonavir) Abbott Laboratories		6 x 100 mg soft gelatin capsules 2 times a day		Nausea; vomiting; diarrhea; loss of appetite; stomach discomfort; oral tingling and numbness; increased liver enzyme levels. Take with meals. Titrated lead-in dosing: start at no less than 300 mg twice a day; increase by 100 mg increments twice a day up to 600 mg twice a day. PATIENT SUPPORT: WWW.NORVIR.COM | 800.222.6885
Viracept® (nelfinavir mesylate) Agouron Pharmaceuticals		2 x 625 mg tablets 2 times a day	5 x 250 mg tablets 2 times a day	Diarrhea (common); nausea; stomach discomfort; gas; rash; increased liver enzyme levels. Tablets now have film coating to prevent early dissolving while swallowing. Take with a meal or light snack. PATIENT SUPPORT: WWW.VIRACEPT.COM | 888.847.2237
NUCLEOTIDES		**STANDARD DAILY DOSING**	**ALTERNATE DAILY DOSING**	**POTENTIAL SIDE EFFECTS/OTHER CONSIDERATION(S)**
Viread® (tenofovir DF) Gilead Sciences, Inc.		1 x 300 mg tablet once a day		Nausea, vomiting, diarrhea, flatulence (intestinal gas). Works best if taken with food, especially a meal containing a small amount of fat. Contraindicated in patients with kidney problems. People with impaired kidney function with a creatinine clearance of less than 60 mL/min should not use tenofovir. Tenofovir increases the levels of ddI by 44%. Recommended dosing: ddI EC 1 x 250 mg capsule once a day when used in combination with tenofovir (see ddI EC above and references). PATIENT SUPPORT: WWW.VIREAD.COM | 800.226.2056
FUSION INHIBITORS		**STANDARD DAILY DOSING**	**ALTERNATE DAILY DOSING**	**POTENTIAL SIDE EFFECTS/OTHER CONSIDERATION(S)**
Fuzeon™ (enfuvirtide, T-20) Roche & Trimeris, Inc.		*ADULTS:* 90 mg subcutaneously, twice daily *CHILDREN (ages 6 to 16):* 2 mg per kg of body weight (maximum 90 mg), twice daily		In the US, Fuzeon is indicated in treatment-experienced patients with evidence of HIV replication despite ongoing antiretroviral therapy. Side effects include: diarrhea, nausea, and fatigue. Clinicians should observe for bacterial pneumonia when Fuzeon is administered. Injection-site reactions have also been reported. Serious allergic reactions are rare, but can include respiratory distress, fever with vomiting, rash, and hematuria. PATIENT SUPPORT: WWW.FUZEON.COM | 877-438-9366

The information contained herein is not intended to be a substitute for professional medical advice. You should not use this information to diagnose or treat a health problem or disease without consulting with a qualified healthcare provider. Please consult your healthcare provider with any questions or concerns you may have regarding your condition.

REFERENCES FOR DAILY DOSING OF ANTIRETROVIRAL AGENTS

GUIDELINES FOR THE USE OF ANTIRETROVIRAL AGENTS IN HIV-INFECTED ADULTS AND ADOLESCENTS (REVISED FEBRUARY 2002) WWW.AIDSINFO.NIH.GO

Kearney BP et al. Didanosine and Tenofovir DF Drug-drug Interaction: Assessment of Didanosine Dose Reduction. Program and Abstracts of the 10th Conference on Retroviruses and Opportunisitic Infections. Boston, MA. February 10-14, 2003. abstract 533. www.retroconference.org

Readers are advised to check the web sites listed in this chart for updates on FDA approved indications and new information on adverse effects and warnings for the use of these drugs.

You can pick up your free copy of NUMEDX, which includes this drug chart, at your local CVS ProCare Pharmacy or your local HIV/Community-based service organization. To find the CVS ProCare Pharmacy nearest you go to www.cvsprocare.com.

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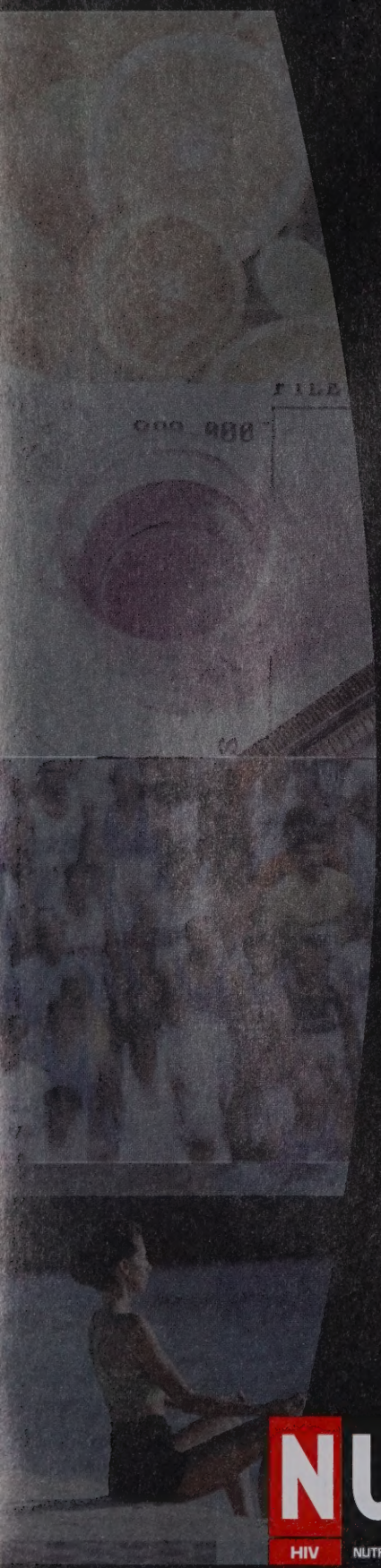

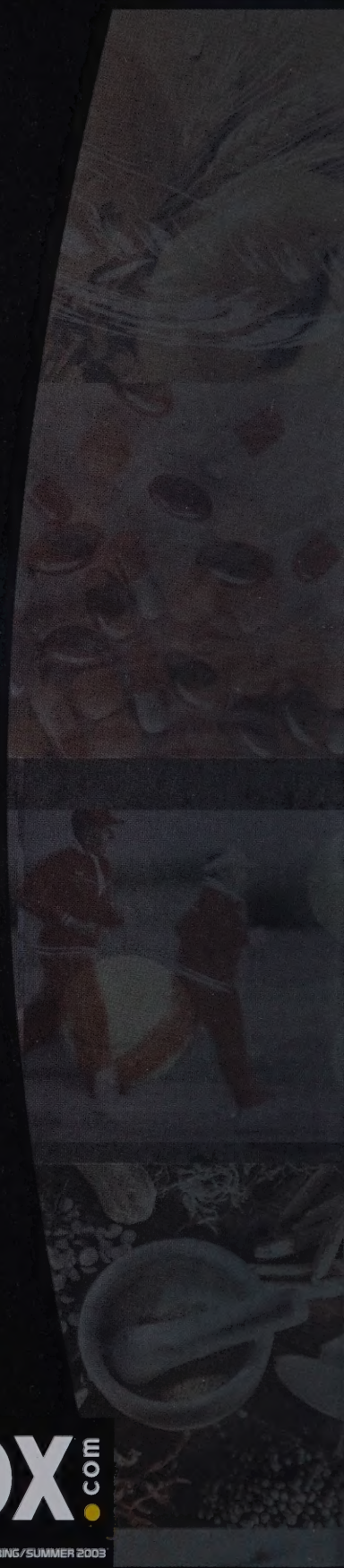

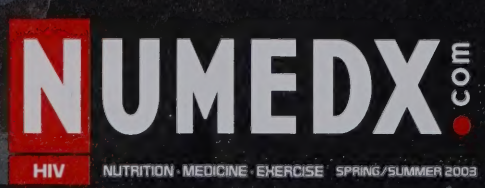

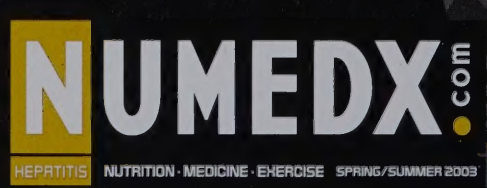

Comparable Antiviral Efficacy of Nevirapine and Efavirenz Over 48 Weeks

BILL VALENTI, MD

Results of the so-called 2NN study, reported at the recent 10th Conference on Retroviruses and Opportunistic Infections (CROI) showed no statistical difference between nevirapine (Viramune®, Boehringer Ingelheim) and efavirenz (Sustiva® , Bristol-Myers Squibb) in anti-HIV efficacy with respect to viral suppression and immune restoration at 48 weeks. 2NN is a large-scale, prospective randomized trial directly comparing non-nucleoside reverse transcriptase inhibitor (NNRTI)–containing regimens in patients initiating anti-HIV therapy.

Study Design

The 2NN study was coordinated by the International Antiviral Therapy Evaluation Center (IATEC) of The Netherlands. The trial enrolled 1216 patients from 65 centers in 17 countries. Treatment-naïve patients received the nucleoside analogues d4T (stavudine—Zerit®; Bristol-Myers Squibb) and 3TC (lamivudine—Epivir®; GlaxoSmithKline), and were randomized to one of four NNRTI treatment arms: nevirapine once-daily; nevirapine twice-daily; efavirenz; and nevirapine + efavirenz. Study participants were required to have a minimum viral load of 5000 copies/mL at study entry; there were no entry restrictions as to baseline CD4+ cell count. Analyses included efficacy, safety, plasma lipid profile, lipodystrophy profile, quality of life, and plasma pharmacokinetics. Results demonstrated the comparable efficacy of nevirapine and efavirenz in HIV.

Results

In the intent-to-treat (ITT) analysis, the most rigorous type of analysis in which noncompleters of the trial are counted as failures, a viral load of <50 copies was reached by 70 percent of the patients in the nevirapine once-daily arm, 65.4 percent in the nevirapine twice-daily arm, 70 percent in the efavirenz arm, and 62.7 percent in the nevirapine + efavirenz arm. The treatment arms had comparable increases in CD4 cells over 48 weeks; these were 170 cells/mm^3 in the nevirapine once-daily arm, 160 cells/mm^3 in both the nevirapine twice-daily arm and the efavirenz arm, and 150 cells/mm^3 in the nevirapine + efavirenz arm in the ITT population. All treatment arms also included the two nucleoside analogue drugs stavudine and lamivudine.

There was no statistical difference in the rates of grade 3-4 serious clinical adverse events or rates of treatment discontinuations in the single NNRTI arms. The most common adverse events experienced in the nevirapine arms were rash and hepatic events, which are the subjects of a black box warning on nevirapine's FDA label (www.viramune.com). The most common adverse events experienced in the efavirenz arms were rash and central nervous system/psychiatric events. The nevirapine once-daily arm had a significantly higher incidence of grade 3 or 4 liver-associated laboratory abnormalities compared to the efavirenz arm.

Results of the 2NN lipid substudy were also presented in a separate presentation. In patients who remained on their allocated treatment (n = 833), a nevirapine-containing regimen resulted in higher levels of HDL-cholesterol (HDL-c; "good" cholesterol). In this substudy, the nevirapine once-daily and twice-daily regimens were analyzed together.

The percentage of HDL-c increase was 37 percent in the nevirapine regimens compared to 24 percent in the efavirenz regimen. In addition, treatment with nevirapine resulted in a significant decrease in the ratio of total cholesterol to HDL-c, an important cardiovascular risk factor. Patients in the nevirapine regimens experienced an 8 percent decrease in cholesterol/ HDL-c ratio, compared to a 1 percent increase in the efavirenz regimen.

The researchers concluded that the results of 2NN demonstrated comparable efficacy between nevirapine and efavirenz, and that nevirapine demonstrated lipid benefits similar to what has been seen in past studies.

A composite end-point comprised of virologic failure, drug discontinuation, HIV disease progression/AIDS, or death was also presented. The percentage of patients who reached the primary end-point was 43.7 percent in the nevirapine twice-daily arm, 43.6 percent in the nevirapine once-daily arm, 37.7 percent in the efavirenz arm, and 53.1 percent in the nevirapine + efavirenz arm. The arm that combined nevirapine + efavirenz was statistically inferior to the efavirenz arm due to decreased tolerability, resulting in more drug discontinuations. There was no statistically significant difference among the other arms.

Cost of drugs was also discussed. According to a Boehringer Ingelheim press release, the price of nevirapine is nearly $2.75 less per day than efavirenz at the US average wholesale price. According to the press release, the US average wholesale price (AWP) of a one-month supply of nevirapine is $366.94 at $12.23 per day. The US AWP of a one-month supply of efavirenz is $449.64 at $14.99 per day. [This information is available at: www.viramune.com or www.boehringer-ingelheim.com/hiv.]

Editor's Notes:
Nevirapine is not indicated for once-daily dosing in the United States. The US FDA-labeled dose of nevirapine for adults is one 200 mg tablet daily for the first 14 days (this lead-in period should be used because it has been found to lessen the frequency of rash), followed by one 200 mg tablet twice daily. Resistant virus emerges rapidly and uniformly when nevirapine is administered alone. For the treatment of HIV-1 infection, nevirapine should

(continued on page 94)

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS	STANDARD DAILY DOSING	ALTERNATE DAILY DOSING	POTENTIAL SIDE EFFECTS/OTHER CONSIDERATION(S)
Rescriptor® (delavirdine mesylate) Agouron Pharmaceuticals Patient Support: www.pfizer.com/hml/hml.html | 888.777.6637	4 x 100 mg tablets 3 times a day or 2 x 200 mg tablets 3 times a day		Rash; headache; fatigue; stomach upset; elevated liver enzymes. Should be taken at least 1 hour before and after didanosine and antacids. Should not be taken with St. John's Wort and many cardiac medications. Please see full prescribing information for the list of contraindicated drugs.
Sustiva® (efavirenz) Bristol-Myers Squibb Patient Support: www.sustiva.com | 800.334.4486	1 x 600 mg tablet Once a day	3 x 200 mg capsules once a day.	Rash, drowsiness, confusion, inability to concentrate, dizziness, vivid dreams, nausea, stomach discomfort, fever, insomnia, elevated liver enzymes. It is recommended that Sustiva be taken on an empty stomach, preferably at bedtime. Increased Sustiva concentrations are seen when this drug is taken with food, which may lead to increase in frequency of adverse events. Dosing at bedtime may improve the tolerability of nervous system symptoms. Women taking this drug should not get pregnant. This recommendation is based on studies which showed congenital malformations in monkeys given this drug; there are no human data available.
Viramune® (nevirapine) Boehringer Ingelheim Patient Support: www.viramune.com | 800.556.8317	1 x 200 mg tablet 2 times a day		Rash; stomach upset; headaches; increased liver function tests. More rarely: hepatitis. Lead-in dosing lessens frequency of rash. For first 14 days: 1 x 200 mg tablet once a day while observing for rash. If no rash develops, dose increased to 1 x 200 mg tablet twice a day.

The information contained herein is not intended to be a substitute for professional medical advice. You should not use this information to diagnose or treat a health problem or disease without consulting with a qualified healthcare provider. Please consult your healthcare provider with any questions or concerns you may have regarding your condition.

Earvin "Magic" Johnson,
diagnosed HIV positive in 1991.

I am not cured

I am partnering with my doctor

I am taking COMBIVIR every day with my other HIV medicines

I am keeping a positive outlook

Individual results may vary.

COMBIVIR does not cure HIV infection/AIDS or prevent passing HIV to others. COMBIVIR should be used with other HIV medicines.

COMBIVIR is a prescription product for HIV and contains two medicines proven to help people with HIV live longer, healthier lives. COMBIVIR is one tablet, taken twice a day, with or without food. COMBIVIR is used in more patients and more major combination studies than any other HIV therapy.

Safety Information

- Make sure to see your doctor regularly because serious side effects can occur, such as muscle damage and a decrease in red and white blood cells
- A buildup of lactic acid in the blood and an enlarged liver, including fatal cases, have been reported
- Low risk of problems with the pancreas in adults and adolescents
- The most frequent side effects are headache, upset stomach, malaise or fatigue, and runny nose

When the time is right for you, ask your doctor about COMBIVIR in combination with other HIV medicines.

Call 1-888-TREAT HIV/Visit www.treatHIV.com

Please see important information about COMBIVIR on adjacent page.

COMBIVIR®
150 mg lamivudine+zidovudine 300 mg
TABLETS

COMBIVIR®
150 mg lamivudine+zidovudine 300 mg
TABLETS

Patient Information about COMBIVIR Tablets

for HIV (Human Immunodeficiency Virus) Infection
Generic name: lamivudine/zidovudine tablets

Please read this information before you start taking COMBIVIR. Staying informed will help you to work more closely with your doctor and healthcare team to determine what is best for you. Remember, this information does not take the place of careful discussion with your doctor. You should remain under a doctor's care when using COMBIVIR and should not change or stop treatment without first talking with your doctor.

What is COMBIVIR?

COMBIVIR is the brand name of a tablet that combines EPIVIR® Tablets (lamivudine tablets) [3TC®] and RETROVIR® (zidovudine) Tablets [ZDV], two drugs which are used to treat HIV (human immunodeficiency virus). HIV is the virus that causes AIDS (acquired immune deficiency syndrome).

How does COMBIVIR work?

COMBIVIR is a combination of lamivudine (la-MIV-u-deen) and zidovudine (Zi-DOHV-u-deen), two medicines (nucleoside analogues) that slow down the replication of the HIV virus. This can reduce the virus' ability to infect new cells. It may help lower the amount of HIV in your body (called "viral load") and raise your CD4 (T) cell count. Lamivudine plus zidovudine when used together can have stronger (synergistic) effects against the virus. COMBIVIR is a convenient way of taking lamivudine and zidovudine. COMBIVIR should usually be taken with other anti-HIV therapy.

Will COMBIVIR work the same as EPIVIR and RETROVIR taken together?

Taking one COMBIVIR Tablet twice a day is the same as taking one EPIVIR 150 mg Tablet twice a day and either two RETROVIR 100 mg Capsules three times a day or one RETROVIR 300 mg Tablet twice a day.

How should I take COMBIVIR?

Take COMBIVIR as your doctor prescribes it. The recommended dose is one COMBIVIR Tablet orally two times a day, with or without food. To help make sure you will benefit from COMBIVIR, you must not skip doses or take "drug holidays."

What should I do if I miss a dose of COMBIVIR?

If you miss a dose by more than 4 hours, wait and then take the next dose at the regularly scheduled time. However, if you miss a dose by less than 4 hours, take your missed dose immediately. Then take your next dose at the regularly scheduled time. Do not take more or less than your prescribed dose of COMBIVIR at any one time.

Does COMBIVIR cure HIV infection or AIDS?

No, there is not a cure for HIV infection or AIDS. People taking COMBIVIR may still develop infections or other illnesses associated with HIV. Because of this, it is very important to remain under the care of a healthcare provider. Use of lamivudine plus zidovudine has been shown to help patients with HIV infection stay healthy and live longer.

Does COMBIVIR reduce the risk of passing HIV to others?

No, COMBIVIR, as well as other HIV medications, has not been shown to reduce the risk of passing HIV to others through sexual contact or blood contamination.

Who should not take COMBIVIR?

You should not take COMBIVIR if you have had a serious allergic reaction to either lamivudine (also known as EPIVIR or 3TC) or zidovudine (also known as RETROVIR or ZDV).

Do not take COMBIVIR at the same time as EPIVIR or RETROVIR, or TRIZIVIR® (abacavir sulfate/lamivudine/zidovudine), because they also contain lamivudine and zidovudine.

Individual dosing with EPIVIR plus RETROVIR, rather than COMBIVIR, should be considered for:

- A child under 12 years of age.
- Anyone who requires dosage adjustments due to drug side effects or poor kidney function.

If you are 65 years of age or over, consult your healthcare professional about the functioning of your liver, kidneys, and heart; about other illnesses you may suffer from, and about any other medications you may be taking. It is possible that the dosage may need to be modified.

What medical problems or conditions should I discuss with my healthcare provider?

Talk to your healthcare provider if:

- You are pregnant or if you become pregnant while taking COMBIVIR. Ask your doctor about enrolling you in the Antiretroviral Pregnancy Registry: 1-800-258-4263.
- You are breast-feeding. Mothers infected with HIV should not breast-feed their infants because HIV is present in breast milk.

Also talk to your doctor about:

- Problems with your blood counts.
- Problems with your muscles.
- Problems with your kidneys.
- Problems with your liver, especially if you have mild or moderate liver disease, such as hepatitis.

Can COMBIVIR be taken with other medications?

Yes. COMBIVIR can be taken with most other medications, including most anti-HIV drugs. Be sure to tell your doctor about all medications, over-the-counter or prescription, that you are taking.

What are the possible side effects of COMBIVIR?

Do not rely on this summary alone for information about side effects. Your healthcare provider can discuss with you a more complete list of side effects that may be relevant to you.

The safety of COMBIVIR is not expected to be different from the safety of EPIVIR and RETROVIR given separately.

In clinical studies of lamivudine plus zidovudine, side effects occurring in 5% or more of patients included: muscle and joint pain, headache, nausea, weakness and fatigue, nasal symptoms, cough, diarrhea, nausea and vomiting, neuropathy, trouble sleeping, fever or chills, loss of appetite, dizziness, abdominal pain or cramps, depression, skin rashes, and indigestion.

It's important to know that serious side effects can occur with COMBIVIR, such as a decrease in red and white blood cells and muscle damage. A buildup of lactic acid and an enlarged liver, including fatal cases, have been reported rarely with some HIV drugs, including nucleoside analogues.

For HIV-infected individuals, periodic blood tests are recommended. If certain changes occur in your laboratory results while you are taking COMBIVIR, particularly if you become anemic or if your white blood cell count falls too low, your medication may need to be adjusted; your doctor may prescribe EPIVIR plus RETROVIR separately in place of COMBIVIR.

Tell your doctor promptly about any side effects or other unusual symptoms you may experience. Although it may make you healthier, COMBIVIR does not cure HIV.

Safety Information

Make sure to see your doctor regularly, because serious side effects can occur, such as muscle damage and a decrease in red and white blood cells. A buildup of acid in the blood, and an enlarged liver, including fatal cases, have been seen. The most frequent side effects are headache, upset stomach, malaise or fatigue, and runny nose.

Other Information

This medication is prescribed for a particular condition. Do not use it for any other condition or give it to anybody else. Keep COMBIVIR and all medicines out of the reach of children.

Like most prescription drugs, lamivudine and zidovudine were required to be tested on animals before they were allowed for human use. In animal studies with doses much higher than those used in humans, zidovudine was associated with vaginal tumors. Your healthcare provider can tell you more about how drugs are tested on animals and what the results of these tests may mean about safety for you.

How should I store COMBIVIR Tablets?

COMBIVIR Tablets may be stored at room temperature and do not require refrigeration.

gsk GlaxoSmithKline

GlaxoSmithKline
Research Triangle Park, NC 27709

This provides a summary of information about COMBIVIR. If you have any questions or concerns about COMBIVIR or HIV, talk to your healthcare provider.

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Emtricitabine (FTC)

BILL VALENTI, MD

Phase III Data Show Emtricitabine Maintains Viral Load Suppression as Part of Once-Daily, Protease-Sparing Anti-HIV Regimen

Recent 48-week data from a Phase III clinical trial has shown that emtricitabine (FTC; Gilead), an investigational once-daily nucleoside reverse transcriptase inhibitor (NRTI), suppresses HIV when taken as part of a once-daily, protease inhibitor (PI)–sparing antiretroviral regimen.

The so-called ANRS 099 Alize trial is an ongoing 3-year, open-label, multicenter study involving 355 patients who at baseline had to have HIV RNA viral loads <400 copies/mL while receiving PI-based antiretroviral therapy. The median duration of PI therapy was 35 months, and the median CD4 cell count was 540 cells/mm^3. Patients were randomized (1:1) to either continue their stable PI-based regimen or switch to an entirely once-daily regimen of emtricitabine, didanosine (ddI—Videx® EC; Bristol-Myers Squibb) and efavirenz (Sustiva® ; Bristol-Myers Squibb).

At 48 weeks, 94 percent of patients receiving the once-daily regimen of emtricitabine, didanosine, and efavirenz had HIV RNA viral load levels <400 copies/mL, compared to 92 percent randomized to continue therapy in the PI-based arm in the intent-to-treat population in which noncompleters are considered failures. When all the samples were analyzed with a more sensitive assay at a central laboratory, the proportion of patients with HIV RNA <50 copies/mL at week 48 was significantly higher in the once-daily treatment group. Ninety-five percent of patients in the once-daily group achieved this result, compared to 87 percent in the PI-based arm (p=.01). The median CD4 cell count increase was comparable in both arms, with an increase of 21 cells/mm^3 for patients on the once-daily regimen and 13 cells/mm^3 for those in the PI-based group.

The discontinuation rate in the study was similar in both arms, with 10.1 percent and 12.4 percent of patients in the once-daily arm and PI-based arm discontinuing, respectively. In addition, patients switching to once-daily therapy with emtricitabine, didanosine, and efavirenz experienced an increase of 7.7 mg/dL in fasting high-density lipoprotein cholesterol (HDL; "good" cholesterol), as compared to no change in the PI-based arm (p<.0001).

Emtricitabine is similar to the currently licensed lamivudine (3TC—Epivir®; GlaxoSmithKline).

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NUCLEOSIDE ANALOGS	STANDARD DAILY DOSING	ALTERNATE DAILY DOSING	POTENTIAL SIDE EFFECTS/OTHER CONSIDERATION(S)
Combivir™ (lamivudine/zidovudine) GlaxoSmithKline Patient Support: www.combivir.com | 888.825.5249	1 x 150 mg lamivudine/ 300 mg zidovudine tablet 2 times a day		Nausea; loss of appetite; headache; fatigue; stomach discomfort (lactic acidosis). More rarely: Muscle wasting; anemia (low red blood cell count); neutropenia (low white blood cell count). Fixed combinations should not be prescribed for patients requiring dose adjusments. Should not be taken with Zerit. Retrovir should not be administered with either Combivir or Trizivir since these agents contain Retrovir as part of their combination formulation.
Epivir® (lamivudine–also known as 3TC) GlaxoSmithKline Patient Support: www.treathiv.com | 800.722.9294	1 x 300 mg tablet once daily	1 x 150 mg tablet 2 times a day	Nausea.
Hivid® (zalcitabine–also known as ddC) of Roche Pharmaceuticals Patient Support: www. rocheusa.com | 800.282.7780	1 x 0.75 mg tablet every 8 hours		Numbness, tingling, or pain in the hands or feet (peripheral neuropathy, seen in 17%–31% patients); nausea; mouth ulcers. Should not be used concomitantly with didanosine. Do not take simultaneously with magnesium/aluminum–containing antacids.
Retrovir® (zidovudine–also known as ZDV or AZT) GlaxoSmithKline Patient Support: www.treathiv.com | 800.722.9294	1 x 300 mg tablet 2 times a day	2 x 100 mg tablets 3 times a day	Taking with food may minimize stomach discomfort. Nausea; stomach discomfort; headache; insomnia. More rarely: muscle wasting; anemia (low red blood cell count); neutropenia (low white blood cell count). Retrovir should not be administered with either Combivir or Trizivir since these agents contain Retrovir as part GlaxoSmithKline of their combination formulation.
Trizivir™ (triple nucleoside–also known as TRZ) combination AZT/3TC/abacavir GlaxoSmithKline Patient Support: www.treathiv.com | 800.722.9294	1 tablet 2 times a day AZT–300 mg 3TC–150 mg abacavir–300 mg		"Strong warning" due to a side effect of abacavir component with up to 5% of patients having a "severe, possibly fatal if untreated, allergic reaction." Area under the curve (AUC) similar to combivir + abacavir in a descriptive study. Careful patient selection for triple nucleoside combination important. Similar side effects to Retrovir (AZT), Epivir (3TC), and Ziagen (abacavir). Do not take if you had an allergic reaction to abacavir.
Videx® EC (didanosine–also known as ddI) Bristol-Myers Squibb enteric coated Patient Support: www.bmsvirology.com | 800.272.4878	>60 kg 400 mg once daily and <60 kg 250 mg once daily	2 x 200 mg capsules Once a day	Numbness, tingling, or pain in the hands or feet (peripheral neuropathy, seen in about 15% of patients); nausea; diarrhea; headache; vomiting; rash. More rarely: pancreatitis. Alcohol may exacerbate toxicity. Avoid aluminum-containing antacids. Preferred formulation for once daily dosing. Take on empty stomach; swallow capsule whole.
Videx® (didanosine–also known as ddI) tablets Bristol-Myers Squibb Patient Support: www.bmsvirology.com | 800.272.4878	2 x 100 mg tablets 2 times a day		Numbness, tingling, or pain in the hands or feet (peripheral neuropathy, seen in about 15% of patients); nausea; diarrhea; headache; vomiting; rash. More rarely: pancreatitis. Alcohol may exacerbate toxicity. Avoid aluminum-containing antacids. Take on an empty stomach 30 minutes before or 2 hours after a meal.
Zerit® (stavudine–also known as d4T) Bristol-Myers Squibb Patient Support: www.bmsvirology.com | 800.272.4878	Patients >60 kg: 1 x 40 mg capsule, every 12 hours. Patients <60 kg: 1 x 30 mg capsule, every 12 hours		Nausea; numbness, tingling, or pain in the hands or feet (peripheral neuropathy). Should not be taken with AZT.
Zerit® XR (stavudine–also known as d4T) Bristol-Myers Squibb Patient Support: www.bmsvirology.com | 800.272.4878	Patients >60 kg 1 x 100 mg once daily Patients <60 kg 1 x 75 mg once daily		No food requirements or restrictions are necessary with Zerit® XR. Side effects, such as slight headache or abdominal pain, are generally mild.
Ziagen™ (abacavir sulfate) GlaxoSmithKline Patient Support: www.ziagen.com | 800.722.9294	1 x 300 mg tablet 2 times a day		Nausea; vomiting; diarrhea; loss of appetite; insomnia. Serious allergic reactions have been reported in about 3%–5% of patients. The signs and symptoms of this reaction include fever, malaise, severe nausea, diarrhea, abdominal pain, sore throat, cough, shortness of breath, and rash. If allergic reaction is diagnosed, therapy should be discontinued and NOT restarted. Symptoms of allergic reactions usually appear within 6 weeks of starting therapy and resolve within 24–48 hours of stopping the drug. A rash without other signs of allergic reaction has also been reported in about 7% of patients. These rashes can usually be managed without stopping therapy. Patients experiencing hypersensitivity reaction (up to 5%) should discontinue the drug and not restart it due to potential life-threatening reactions.

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Protease Inhibitors in the Pipeline

BILL VALENTI, MD

Two new protease inhibitors (PIs) are currently in the pipeline: Atazanavir (BMS AI424-034; Bristol-Myers Squibb) and Fosamprenavir (GW 433908; GlaxoSmithKline). Of these two drugs, described below, Atazanavir is the farthest along in clinical trials and has an early access program (EAP). Also, both drugs appear to have less adverse impact on lipids, in contrast to some of the currently available PIs.

Atazanavir (BMS AI424-034)

This two-arm multinational trial of 805 patients was designed to demonstrate equivalence in response, not superiority, for the atazanavir arm (400 mg once daily) compared to the efavirenz arm (Sustiva®; Bristol-Myers Squibb). All patients were antiretroviral treatment–naïve with CD4 counts above 100 cells/mm^3 and with an enrollment viral load of >2000 copies RNA/mL. In addition to the study drug, patients also received AZT and 3TC (Retrovir® and Epivir®, respectively; both GlaxoSmithKline) given in fixed dose combination (Combivir®; GlaxoSmithKline).

The primary outcome of the study was a viral load <400 copies/mL plasma. At 48 weeks, 84 percent and 80 percent of subjects remained on therapy; viral loads <400 copies were 70 percent and 64 percent in the atazanavir and efavirenz arms, respectively. Also, atazanavir had significantly fewer negative effects on cholesterol and triglyceride levels compared to efavirenz.

Additional analyses of subsets of patients—including those with baseline viral load measurements above or below 100,000 copies, and males compared to females—did not reveal any statistically significant differences between these two treatment arms. Thus it appears that this study demonstrated that Combivir + atazanavir was equivalent to Combivir + efavirenz.

Atazanavir's EAP is for patients who are failing their current antiretroviral therapy (i.e., who have an HIV RNA level >5000 copies/mL and an absolute CD4 count <300 cells/mm^3) and who are unable to construct an alternative treatment regimen using other available antiretroviral agents due to prior virologic failure and/or drug intolerance. This program will also provide atazanavir to patients who have severe HAART-associated hyperlipidemia, despite lipid-lowering therapy, defined as a triglyceride level >750 mg/dL or a cholesterol level meeting National Cholesterol Education Program guidelines for use of a lipid-lowering agent. (See the discussion of Lipids and Cardiovascular Risk elsewhere in this issue.)

Patients may be enrolled in the EAP through their physicians only by calling toll free 1-877-726-7327.

Squires KE, Thiry A, Giordano M, for the AI424-034 International Study Team. Atazanavir (ATV) QD and efavirenz (EFV) QD with fixed-dose ZDV+3TC: Comparison of antiviral efficacy and safety through week 24 (AI424-034). Program and Abstracts of the 42nd Interscience Congress on Antimicrobial Agents and Chemotherapy; September 27–30, 2002; San Diego, California. [Abstract H-1076]

Fosamprenavir (GW 433908)

The investigational PI called GW 433908, also known as 908 or fosamprenavir, is the calcium

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PROTEASE INHIBITORS	STANDARD DAILY DOSING	ALTERNATE DAILY DOSING	POTENTIAL SIDE EFFECTS/OTHER CONSIDERATION(S)
Agenerase™ (amprenavir) GlaxoSmithKline Patient Support: www.treathiv.com | 800.722.9294	8 x 150 mg capsules twice a day	8 x 150 mg amprenavir with 2 x 100 mg ritonavir once daily or 4 x 150 mg amprenavir with 1 x 100 mg ritonavir twice daily.	Rash (seen in 20% of patients); diarrhea; nausea; vomiting; oral tingling and numbness. High fat meals should be avoided. Should be taken at least 1 hour before or after didanosine and antacids. Vitamin E supplements should not be taken with amprenavir. For usage with Methadone and/or oral (hormonal) contraceptives see http://www.fda.gov/cder/foi/label/2002/21007s11,21039s10lbl.pdf
Crixivan® (indinavir) Merck & Co. Patient Support: www.crixivan.com | 800.850.3430	2 x 400 mg capsules every 8 hours	2 x 400 mg capsules of Crixivan with 2 x 100 mg soft gelatin capsules of Norvir 2 times a day; 1 x 400 mg capsules of Crixivan with 4 x 100 mg soft gelatin capsules of Norvir 2 times a day	Kidney stones (seen in 6%–8% of patients); nausea; vomiting; diarrhea; stomach discomfort; headache; insomnia; rash; back pain. Take on empty stomach 1 hour before or 2 hours after a meal. Drink at least 8 glasses of water daily.
Fortovase® (saquinavir) Roche Pharmaceuticals Patient Support: www.fortovase.com | 800.910.4687	6 x 200 mg soft gelatin capsules 3 times a day	5 x 200 mg Fortovase with 1 x 100mg ritonavir twice daily or 8 x 200 mg Fortovase with 1 x 100 mg ritonavir once daily or 5 x 200 mg Fortovase with 3 lopinavir/ritonavir (Kaletra) twice daily.	Nausea; diarrhea; stomach discomfort; insomnia; headache; increased liver enzyme levels. Take within 2 hours after a full meal. Saquinavir taken without food may have less bioavailability.
Invirase® (saquinavir mesylate–gel caps) Roche Pharmaceuticals Patient Support: www.rocheusa.com | 800.910.4687	3 x 200mg capsules 3 times a day Boosted dose with ritinovir highly recommended. See alternative dosing box.	5 x 200 mg Invirase with 1 x 100 mg ritonavir twice daily or 8 x 200 mg Invirase with 1 x 100 mg ritonavir once daily or 5 x 200 mg Invirase with 3 lopinavir/ritonavir (Kaletra) twice daily.	Diarrhea, abdominal discomfort and nausea. Take 2 hours after a full meal. Do not take with grapefruit juice. Do not take with astemizole (Hismanal), terfenadine (Seldane), ergotamine (Cafergot), D.H.E. 45 or midazolam (Versed), or triazolam (Halcion).
Kaletra™ (lopinavir/ritonavir) Abbott Laboratories Patient Support: www.kaletra.com | 800.222.6885	3 x 133 mg lopinavir/33 mg ritonavir capsules 2 times a day		Second generation protease inhibitor. Combines lopinavir (133.3 mg) and Ritonavir (33.3 mg). Same drug interactions and side effects as with ritonavir. During clinical trials, side effects reported were diarrhea of mild to moderate severity (14%–24%), nausea/vomiting (2%–15%/1.6%–5%), and abnormal stools (1%–6%).
Norvir® (ritonavir) Abbott Laboratories Patient Support: www.norvir.com | 800.222.6885	6 x 100 mg soft gelatin capsules 2 times a day		Nausea; vomiting; diarrhea; loss of appetite; stomach discomfort; oral tingling and numbness; increased liver enzyme levels. Take with meals. Titrated lead-in dosing: start at no less than 300 mg twice a day; increase by 100 mg increments twice a day up to 600 mg twice a day.
Viracept® (nelfinavir mesylate) Agouron Pharmaceuticals Patient Support: www.viracept.com | 888.847.2237	2 x 625 mg tablets 2 times a day	5 x 250 mg tablets 2 times a day	Diarrhea (common); nausea; stomach discomfort; gas; rash; increased liver enzyme levels. Tablets now have film coating to prevent early dissolving while swallowing. Take with a meal or light snack.

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Tenofovir: Update on Use in Treatment-Naïve Patients

DAVID J. STERKEN, MN, CNS, CPNP | BILL VALENTI, MD

Tenofovir (Viread®, Gilead Sciences, Inc.) is the first in a new class of HIV medications called nucleo**tide** reverse transcriptase inhibitors. It acts in much the same way as nucleo**side** reverse transcriptase inhibitors (e.g., AZT or Retrovir®, GlaxoSmithKline; 3TC or Epivir®, GlaxoSmithKline; d4T or Zerit®, Bristol-Myers Squibb) by preventing HIV from entering the nucleus of healthy CD4 cells (T-helper cells). At the cellular level, nucleoside reverse transcriptase drugs (NRTIs) work by blocking a viral enzyme, reverse transcriptase. This enzyme is vital to the conversion of HIV RNA into DNA. The major difference between nucleoside and nucleotide analogs is that nucleotides are chemically pre-activated and require less biochemical processing to become active.

Background

Tenofovir was approved by the US Food and Drug Administration (FDA) in October 2001 for the treatment of HIV disease. It was approved in February 2002 for use in all member states of the European Union. The initial efficacy and safety testing for the drug was in treatment-experienced patients rather than in antiretroviral-naïve patients. This "salvage therapy" approach was used in Phase II and III clinical trials on subjects who were experiencing viral breakthrough (insufficient viral suppression) on existing HAART regimens. In each of these studies, the viral load decreases were statistically significant with low levels of toxicity.[1,2]

Additional data from the Gilead 903 study compared tenofovir with stavudine, both combined with lamivudine and efavirenz, in 600 treatment-naïve subjects with relatively high viral loads at baseline (mean, 81,300 copies/mL).[3] Only 9 percent of subjects had discontinued at 48 weeks, and 82 percent of tenofovir recipients and 81 percent of stavudine-treated subjects had plasma HIV-1 RNA levels <50 copies/mL. In terms of the metabolic effects of these agents, during 48 weeks of therapy, the mean changes in triglycerides, total cholesterol, and LDL cholesterol were significantly lower in the tenofovir arm at 48 weeks. The change in HDL cholesterol was not different between treatment arms.

Resistance Profile

One of the challenges of continued Highly Active Antiretroviral Therapy (HAART) is drug resistance, or decreased sensitivity of the virus to a drug or combination of drugs. Tenofovir's powerful anti-HIV activity stems from its unique resistance profile.[1] Miller et al. found tenofovir to be active against multinucleoside-resistant HIV expressing HIV the "Q151M mutation, but [showing] reduced susceptibility to the T69S insertion mutations."[4] Cheonis also reports that resistance to tenofovir "appears to be reversed by the M184V mutation selected by 3TC."[1] The partial resistance to tenofovir seems to have been associated with the K65R mutation, a similar resistance pattern seen with abacavir (Ziagen™, GlaxoSmithKline) and ddI (Videx®, Bristol-Myers Squibb). In blinded analysis, however, it is not known whether this mutation is due to the presence of abacavir or ddI in the subjects' treatment regimen.[5] Miller et al., however, noted that in the three cases of tenofovir-associated resistance, none experienced viral rebound by week 24.[4]

Side Effects

Tenofovir appears to be a drug with few short-term side effects based on experience to date. The most common side effects are gastrointestinal events (nausea, vomiting, diarrhea, flatulence), weakness, and abdominal pain; precautions include renal impairment, lactic acidosis, and severe hepatomegaly with steatosis (enlarged liver with fat accumulation) and osteomalacia.[2,6,7]

Bone toxicity (osteomalacia) has been noted in animal studies using high doses of tenofovir. Although the dose in animal studies is higher than doses given to humans, consultants on bone metabolism at the FDA approval hearing made the following recommendations to the FDA Advisory Committee:

- That Gilead Science do further research to identify the potential mechanism causing the osteomalacia (lack of normal mineralization of the bone)—was the problem due to a deficiency of the minerals in the body or was tenofovir interfering with the enzymes needed for bone mineralization?[6]
- That baseline studies be performed looking for vitamin D deficiency and nutritional problems.[6]

Williams and Pujol report that the bone toxicity or impairment is most likely associated with a phosphorus deficiency induced or caused by tenofovir.[7] "Phosphorus plays an important role in converting vitamin D to its biologically active form, which is required in order for the body to absorb calcium, needed for the development and maintenance of bone."[7] Hypophosphatemia has the potential to create an electrolyte imbalance (increased sodium, chloride, calcium, water; decreased potassium, magnesium, nitrogen) and the body attempts to compensate by pulling calcium from the bones. Williams and Pujol recommend that patients taking tenofovir eat meat or another protein source (dried beans, eggs) with every meal to help maintain phosphorus levels.[7] Grains and cereals are also good sources of phosphorus.

Although renal toxicity has not been observed in clinical studies, the clinician should carefully monitor renal function tests. This precautionary measure is suggested in light of the renal toxicity, namely renal proximal tubular damage, found to be a major side effect in two other nucleotides—cidofivir (licensed) and adefovir (development for HIV discontinued). Although tenofovir is transported by the same mechanism, renal toxicity has not been observed.[2]

The long-term effects of tenofovir, including the risk of mitochondrial dysfunction and body shape changes, are not known. Safety and potency have not been tested in children.

Dose

The recommended dose of tenofovir is 300 mg once daily. It should be taken in combination with other anti-HIV drugs. If you are taking ddI with tenofovir, take ddI EC (Videx EC) 250 mg once daily. See drug interactions below.

Food Restriction

Tenofovir should be taken with food, preferably a full meal containing some fat.

Who Should NOT Take Tenofovir (Viread)?

- Persons with a history of kidney problems
- Pregnant women
- Breastfeeding mothers

Drug Interactions

- Tenofovir increases the levels of ddI in your blood. As a result, patients may experience increased ddI side effects (pancreatitis, peripheral neuropathy, hepatitis).
- If you are taking ddI with tenofovir, take ddI EC (Videx® EC, Bristol-Myers Squibb) 250 mg once daily.
- There is some evidence that tenofovir may work better in persons whose virus is resistant to lamivudine; some doctors recommend taking the two drugs together.
- Tenofovir is eliminated by the kidneys and may interact with other drugs that are eliminated by the kidney (acyclovir, valacyclovir, ganciclovir, and valgancyclovir).
- Tenofovir should definitely not be taken with cidofivir (recommendation of Gilead Science).

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NUCLEOTIDES	STANDARD DAILY DOSING	ALTERNATE DAILY DOSING	POTENTIAL SIDE EFFECTS/OTHER CONSIDERATION(S)
Viread® (tenofovir DF) Gilead Sciences, Inc. Patient Support: www.viread.com | 800.226.2056	1 x 300 mg tablet once a day		Nausea, vomiting, diarrhea, flatulence (intestinal gas). Works best if taken with food, especially a meal containing a small amount of fat. Contraindicated in patients with kidney problems. People with impaired kidney function with a creatinine clearance of less than 60 mL/min should not use tenofovir. Tenofovir increases the levels of ddI by 44%. Recommended dosing: ddI EC 1 x 250mg capsule once a day when used in combination with tenofovir (see ddI EC above and references).

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Fusion Inhibitors: A Progress Report

DAVID RUBIN, MD

A new class of antiretroviral agents (ARVs) has stirred strong interest among clinicians and patients. The first fusion inhibitor, T-20 or enfuvirtide (Fuzeon®, Roche), heralds an era in which new viral targets are used to suppress viral replication, potentially reducing long-term toxicities and avoiding cross-resistance with currently available ARVs. In this review, we will briefly examine new agents and strategies to inhibit viral entry into the CD4(+) cell, and then focus on the most advanced agent in clinical development, enfuvirtide, and its potential value in our anti-HIV armamentarium.

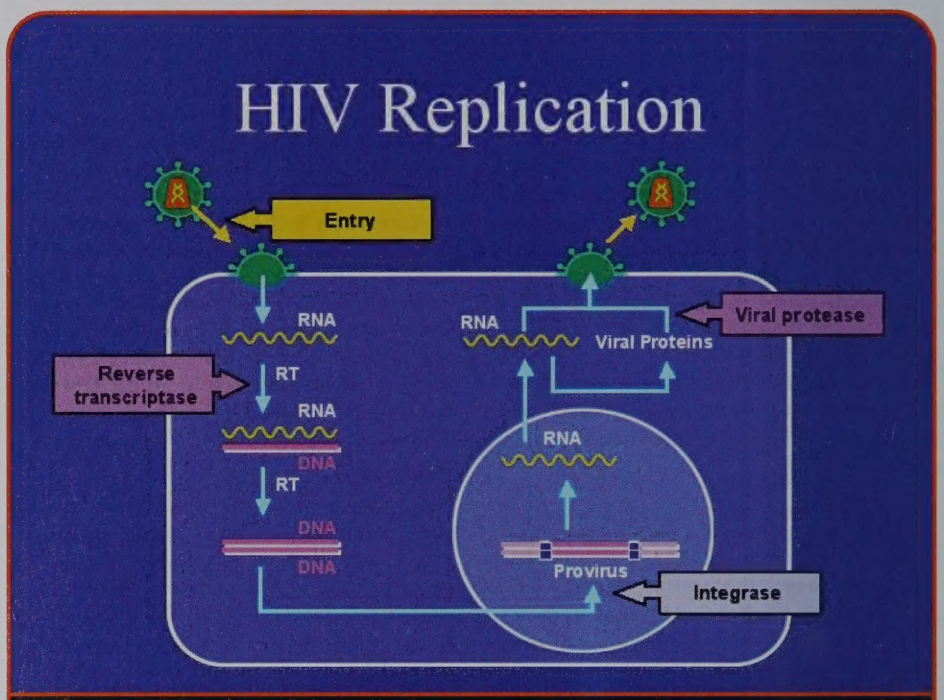

Diagram 1

As noted in diagram 1, the two current viral enzyme targets for our ARV agents are reverse transcriptase and protease, which represent important steps in viral replication once the CD4(+) cell is already infected. New targets involving the prevention of initial viral entry into the cell have been explored at three distinct steps of virus–cell interaction (see diagrams 2 and 3): binding of the viral envelope protein gp120 to the CD4(+) receptor molecule on the cell surface; binding of the viral envelope to the chemokine co-receptor molecule; and fusion of the viral and cellular membranes.

To briefly summarize the work done to date on CD4-receptor and chemokine receptor inhibition, we need to examine data on PRO542, SCH-C, and AMD3100. PRO542 is a monoclonal antibody containing CD4 receptor domains with an immunoglobulin backbone currently in Phase I/II pediatric study delivered by IV infusion. SCH-C has potent activity against CCR5-predominant virus with excellent oral bioavailability; however, it has the potential for QTc prolongation at high doses. AMD3100 has evidence of antiretroviral activity against CXCR4-predominant virus; however, development has been halted due to unfavorable pharmacokinetics.

Inhibition of the step in which fusion of viral and cellular membrane occurs is nearing clinical availability with the development of enfuvirtide, a 36-amino-acid peptide subcutaneously (sc) administered twice daily. Put as simply as possible (see diagrams 4 and 5): there are two heptad repeat portions of gp41 (HR) that, when engaged after the gp120-chemokine receptor binding occurs, serve to pull the viral envelope towards the cell membrane to allow the two entities to fuse. If the interactions of HR-1 and HR-2 can be inhibited, thus "jamming" the launching mechanism of HR-2, then gp41 cannot fuse with the cell membrane. Both enfuvirtide and T-1249 are peptides with amino-acid sequences that are identical to or very similar to regions of the HR-2 portion of the gp41 molecule and act to inhibit the gp41-cell membrane interaction (see diagram 6).

Data presented by Roche/Trimeris on two international trials named TORO 1 and 2 demonstrate both efficacy and safety in a cohort of heavily treated, advanced patients. A preliminary analysis after 24 weeks of observation was first presented at the 14th International Conference on AIDS held in Barcelona during July 2002. These pivotal trials conducted in North America, Mexico, and Brazil through TORO 1 and in Europe and Australia through TORO 2 were open-label, randomized 2:1 to either a control group of "optimized background" (OB) of ARVs or a group treated with enfuvirtide + OB. Patients who were enrolled were

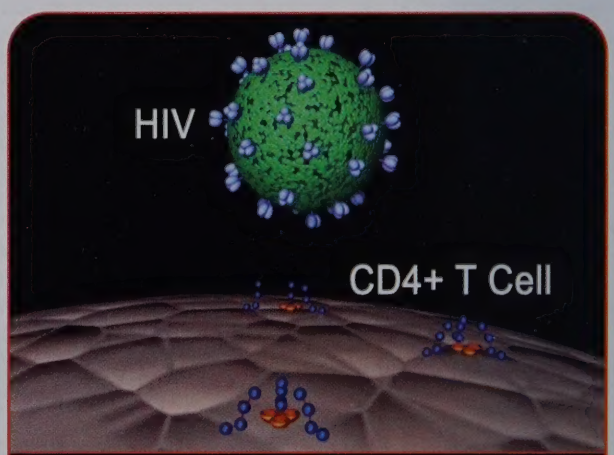

Diagram 2

required to have had HIV RNA >5000, at least 3–6 months of prior experience with each of the existing classes of agents, or documented viral resistance. Each patient was placed on an optimized regimen based on both history of prior ARV exposure and/or results of resistance assays. The dose of enfuvirtide used was 90 mg sc twice daily. In both trials, the demographics and baseline characteristics were similar: median RNA, 5.1–5.2 logs; CD4 count, 80–98; median number of prior ARVs, 12; median years of ARV use, 7.0–7.4; number of drugs in the OB regimen to which the virus was phenotypically sensitive, 1.4–1.7.

In the initial ITT (intent to treat) analysis, one of the strictest methods of analyzing data, out of 995 patients enrolled in the trials, 135 (13.6%) prematurely discontinued, most due to adverse events related to the drugs used in the trial. Most interestingly, there were no significant excess adverse events noted in either the OB or the OB + enfuvirtide groups with the exception of injection-site reactions (ISRs) related to enfuvirtide. These ISRs were described as tender erythematous nodular lesions initially presenting within the first week, necessitating rotation of the injection site. Although 95.7 percent of patients receiving the drug in TORO 1 experienced ISRs, approximately 50 percent reported only mild tenderness at the injection site (grade 1); 42 percent reported moderate pain with no limitation of daily activities (grade 2). Pain or discomfort requiring analgesics or limiting of usual activities occurred in less than 10 percent of patients. Most patients learned to manage ISRs over the course of the 24-week observation period; only 17 percent reported any individual lesions lasting longer than 1 week. Notably, only 24 (3%) patients dropped out of the trials because they experienced ISRs.

In the efficacy analysis of TORO 1 and 2, a primary study endpoint ITT analysis at 24 weeks revealed a difference of 0.93 log between enfuvirtide-treated and control groups in TORO 1 and a 0.78 log difference in TORO 2. Secondary analysis showed statistically significant RNA decreases from baseline and statistically significant greater proportions of patients with RNA <400 and <50 in the treated group. Also, the CD4 count change from baseline was statistically significant, favoring the enfuvirtide group.

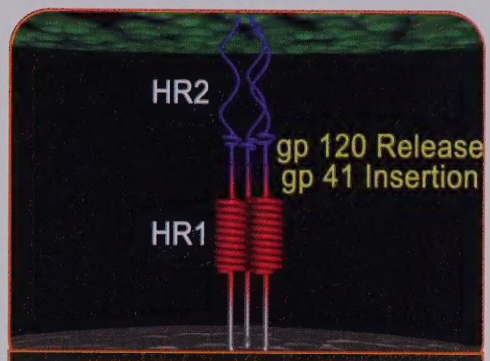

Diagram 3

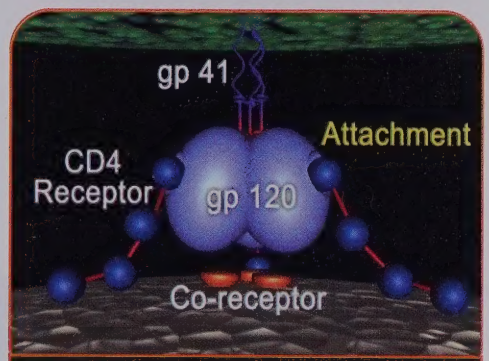

Diagram 4

Diagram 5

At the 42nd ICAAC Conference held in San Diego in September 2002, further subanalysis of TORO 1 was presented. Predictors of virologic response, other than receipt of enfuvirtide, were a higher baseline CD4 cell count, a higher phenotypic or genotypic sensitivity score, patient adherence, and inclusion of lopinavir/ritonavir in the new regimen.

Prior use of lopinavir/ritonavir was associated with a reduced likelihood of achieving a virologic response, whereas baseline viral load was not a significant predictor of response. At the 6th International Congress on HIV Drug Therapy held in Glasgow, Scotland in November 2002, further subanalysis of TORO 2 revealed superior efficacy for enfuvirtide regardless of gender, race, or age. Prior use of lopinavir/ritonavir was, again, associated with treatment failure. Interestingly, although patients with few mutations to either RT or protease may not have seen greater benefit with this agent, those patients with >4 mutations of any kind showed better response to enfuvirtide-containing regimens.

Work done by Trimeris has elucidated the correlates of resistance to enfuvirtide associated with amino-acid substitutions within the gp41, having less effect on T-1249. At present, in-vitro work has yet to generate resistance to T-1249 in wild-type HIV.

Availability of enfuvirtide is limited by the complexity of synthesizing significant amounts of this compound for clinical use. This may result in limited availability of this agent initially. There is also the practical consideration of training patients to re-suspend the powder form of the drug into a diluent with each injection.

T-1249 is a second-generation peptide fusion inhibitor now in clinical development. In vitro studies suggest that this agent appears more active against wild-type virus than is enfuvirtide; it is more resistant to the development of mutations; and it retains its activity against viral variants that have decreased susceptibility to enfurvirtide. Animal studies suggest the possibility of once-daily dosing. A single clinical Phase I/II study for 14 days in a small cohort demonstrated that T-1249 was well tolerated, with a somewhat lower occurrence of ISRs compared to enfuvirtide. Dosing of the agent is still in development because the maximum-tolerated dose has not yet been reached and additional higher dosing cohorts are being entered into trials.

Fusion Inhibitors: A Progress Report *(continued)*

DAVID RUBIN, MD

Looking toward the future, the promise of potential synergy between multiple agents blocking HIV entry into the cell, particularly the combination of a chemokine-receptor blocker with a fusion inhibitor, is intriguing. By blocking the viral-chemokine receptor interaction, fusion inhibition may be potentiated by a longer period of contact between gp41 and such agents as enfuvirtide and T-1249. However, the greatest challenge to the use of enfuvirtide at present is the threat that resistance will develop to the drug unless it can be combined with other agents that have at least some residual activity.

Dr. David Rubin is the Medical Director of the AIDS Center of the New York Hospital of Queens and has a private practice dedicated to the care of HIV-infected patients. Dr. Rubin also serves on multiple committees for the NY State Dept. of Health and is the current Chairman of the Clinical Advisory Board of NY State ADAP. N

Editor's Note: Enfuvirtide has been approved for use by the US Food and Drug Administration.

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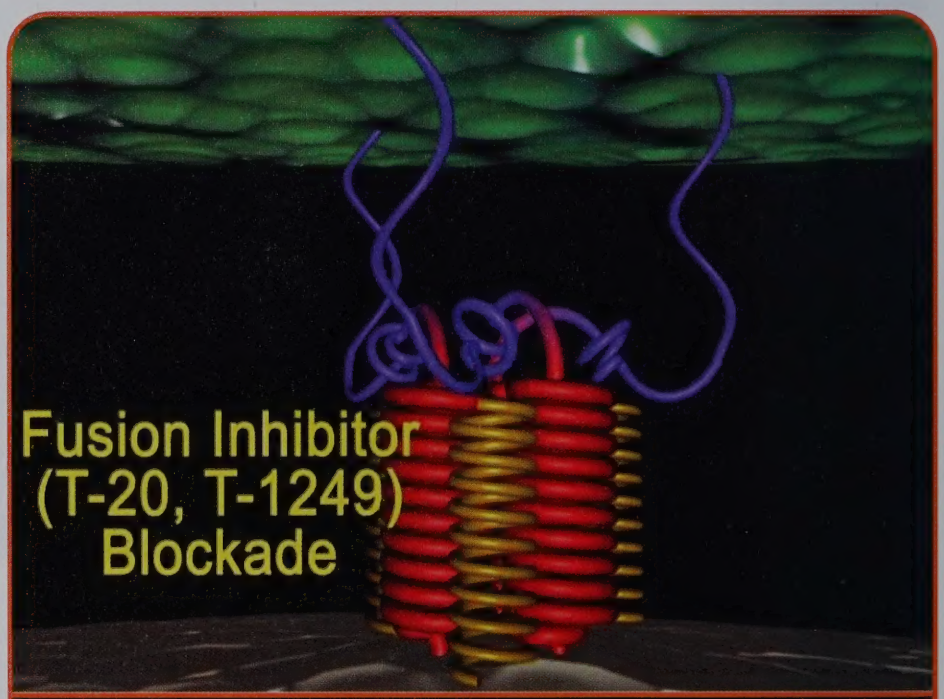

Diagram 6

FUSION INHIBITORS	STANDARD DAILY DOSING	ALTERNATE DAILY DOSING	POTENTIAL SIDE EFFECTS/OTHER CONSIDERATION(S)
Fuzeon™ (enfuvirtide, T-20) Roche & Trimeris, Inc.	*ADULTS:* 90 mg subcutaneously, twice daily *CHILDREN (ages 6 to 16):* 2 mg per kg of body weight (maximum 90 mg), twice daily		In the US, Fuzeon is indicated in treatment-experienced patients with evidence of HIV replication despite ongoing antiretroviral therapy. Side effects include: diarrhea, nausea, and fatigue. Clinicians should observe for bacterial pneumonia when Fuzeon is administered. Injection-site reactions have also been reported. Serious allergic reactions are rare, but can include respiratory distress, fever with vomiting, rash, and hematuria.

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Once-a-Day Therapy: Now or Later?

TONY ADINOLFI, MSN, RN, CNS, ANP, ACRN

There are now 21 drugs available to slow down the replication of HIV in humans. We have learned great lessons over the years and still have many questions unanswered.

In this article, the concept of once daily therapy for HIV infection will be discussed. First, in order to have virologic suppression of HIV, adherence of 95 percent or higher to HIV therapy is required.[1] Suboptimal adherence leads to treatment failure. We have learned from other chronic conditions that when the pill regimen is simple, adherence is improved. Patients taking antihypertensive medications had improved adherence with increasing regimen simplicity. Ninety percent were adherent to once daily regimens, 80 percent were adherent to twice daily regimens and 65 percent were adherent to three times daily or greater regimens.[2] We can generalize from the hypertension studies that as regimens for HIV become simpler, medication adherence will improve.

What are some reasons why patients don't adhere to their regimen? Answers that have been given include: every time the pills are taken it is a reminder that the person has HIV; fear of getting caught by family, friends or coworkers; not knowing where one will be or having to adhere to a rigid schedule; simple forgetfulness; side effects; and too many pills to swallow.[3] Another reason involves certain food restrictions or requirements. In Bartlett's meta analysis of adherence, he found that as the number of pills in a regimen increased, the chances of virologic suppression decreased.[4]

Factors that Determine Treatment Adherence

- The patient
- Tolerability
- Preference
- Regimen
- Pill
- Complexity
- Burden
- Dosing
- Frequency

The move to once-daily dosing is gaining popularity among treatment-experienced and treatment-naïve patients. Table 1 summarizes the state of the art in terms of once daily antiretrovirals.

A drug should be powerful enough to work (i.e., it should have a long enough half-life) even if a person misses a dose. Combination therapies must also have a side effect profile that does not interfere with the patient's quality of life. The following drug combinations of FDA-approved drugs are in common once daily use. The combinations continue to be studied for safety, tolerability, convenience, and viral suppression. Preliminary reports suggest these combinations can be taken once daily and are effective in reducing the viral load and in maintaining CD4 cell count. Please check the pullout drug chart in this issue or the product information for the correct dosages of the following medications:

- Didanosine (Videx® EC) + tenofovir (Viread®) + efavirenz (Sustiva®). When tenofovir (Viread®) and didanosine (Videx®) are given together, there is a 50 percent increase in didanosine's area under the curve (AUC). The current recommendation from the manufacturers is to take didanosine as Videx® EC 250 mg once daily with tenofovir.
- Didanosine (Videx® EC) + lamivudine (Epivir®) + efavirenz (Sustiva®) once-daily.
- Tenofovir (Viread®) + lamivudine (Epivir®) + efavirenz (Sustiva®).
- Didanosine (Videx® EC) + tenovofir (Viread®) + boosted amprenavir (Agenerase®).
- Tenofovir (Viread®) + lamivudine (Epivir®) + saquinavir, hard gel capsules (Invirase®) + ritonavir (Norvir®).
- Didanosine (Videx, EC) + lamivudine (Epivir®) + boosted amprenavir (Agenerase®) + ritonavir (Norvir®).
- Didanosine (Videx® EC) + lamivudine (Epivir®) + nevirapine (Viramune®) once daily.

A new protease inhibitor, Atazanavir (2 tablets once daily), is in Phase III clinical trials. Other drugs are being studied for once-daily use, but their once daily efficacy has not been proven and such use is considered "off-label." These drugs include zidovudine (Retrovir®) (2 tablets once daily without food restrictions), abacavir (Ziagen®), and lopinavir/ritonavir (Kaletra®) (6 capsules once daily with food).[7]

Patients should consult with their healthcare provider and not make treatment decisions based solely on how easy the regimen will be. All factors should be taken into consideration. For providers, getting to know the patient before prescribing any regimen is essential. It is important to understand what kind of schedule the person has, what other medications they may be taking, their ability to swallow pills (many of the medications come in a liquid form and that is also an option for those who have trouble swallowing pills), how high their viral load is, and how low their CD4 cell count is.

There are many HIV medications available to patients. The medications only work if the patient takes them as directed. With the availability of once daily therapy, many people who have had difficulty with adherence due to dosing frequency, regimen complexity, pill burden, and tolerability now have other options available to them.

From studies with other medications, we know that by reducing pill burden and by simplifying regimens and dosing frequency, patients can have a good response to their medications. HIV can be kept in check and people taking medications can lead a long and healthy life.

Tony Adinolfi, MSN, RN, CNS, ANP, ACRN is an assistant clinical professor of nursing at the Duke University School of Nursing and an Adult Nurse Practitioner with the Division of Infectious Diseases at Duke Medical Center, caring for patients in outreach clinics. N

TABLE 1. Once Daily Antiretroviral Drugs

FDA-approved for once daily use	Approved agents under once daily evaluation	Investigational agents
Nucleosides		
Lamivudine (Epivir®)	Abacavir (Ziagen®)	Emtricitabine (FTC)
Stavudine XR (Zerit® XR)	Zidovudine	
Didanosine EC (Videx® EC)		
Nucleotides		
Tenofovir (Viread®)		
Non-Nucleosides		
Efavirenz (Sustiva®)		
Protease Inhibitors (PIs)		
Boosted amprenavir (Agenerase®)	Lopinovir/ritonavir (Kaletra®)	Atazanavir (Zrivada®)
	Other boosted PIs [5,6]	

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"Sometimes It Really Is a Zebra" Anemia in HIV Disease: A Case Study

RICHARD S. FERRI, PHD, ANP, ACRN, FAAN

Anemia remains a frequent complication in HIV disease even in the era of combination therapy. Also, newer treatments for co-infection with hepatitis C may increase the incidence of anemia in clinical practice. The following is an actual case study.

Case Information

The patient is a 42-year-old female with acquired immunodeficiency syndrome (AIDS). She presents with a 2-week history of flulike symptoms—fatigue, slight shortness of breath, aching joints, and diffuse itching. She reports strict adherence to her antiretroviral regime by direct questioning. Symptoms have been waxing and waning.

Past Medical History

The patient tested positive for the human immunodeficiency virus (HIV) in 1999 with a presenting illness of unresolving bacterial pneumonia and oral candidiasis. Her CD4 count was 179/mm^3 with a viral load of greater than 750,000 copies. She was started on efavirenz (Sustiva®, Bristol-Myers Squibb) 600 mg QHS and zidovudine/lamivudine (Combivir®, GlaxoSmithKline) one tablet twice daily to treat her HIV disease.

She was also started on pneumocystis carinii pneumonia (PCP) prophylaxis—sulfamethoxazole 800 mg/trimethoprim 160 mg (Bactrim DS®) one tablet daily. Her bacterial pneumonia resolved within 2 weeks after starting antiretroviral therapy and a 10-day course of clarithromycin (Biaxin®) 500 mg twice daily. PCP prophylaxis was discontinued after 12 months of stable CD4 counts greater than 200/mm^3 and undetectable viral loads.

The patient had an excellent virologic response to her antiretroviral regimen that resulted in a CD4 count of 425/mm^3 and a viral load that was less than 400 copies.

- Gravida 1 Para 1.
- No other significant medical history.
- No history of injection drug use or tobacco abuse. Patient drinks alcohol socially.

Family History

Noncontributory.

Social History

The patient is a former flight attendant; she is presently on disability and is not working. Her partner is also HIV-positive and continues to work. She has one 3-year-old child who has tested HIV-negative.

Current Medications

- No known drug allergies
- Efavirenz (Sustiva®) 600 mg at bedtime
- Zidovudine/lamivudine (Combivir®) 1 tablet twice daily
- Multivitamins 2 tablets daily

Laboratory Values at Initial Office Visit

HIV Viral load: <50 copies/mL
CD4+: 589/mm^3

Hematology	Normal Range
Hb 6.2 g/dL	13.2–16.9
Hct 18.7%	38.5–49
MCH 18.1 pg	27–33.5
MCV 126 fL	80–97
WBC 3.45 x 10^3/mm^3	3.9–11.1
RDW 15.2%	11.0–15.0
RBC 2.28 x 10^6/mm^3	4.20–5.70
Plts 172 x 10^3/mm^3	140–390

Assessment

S: 42-year-old female in moderate distress. Very pale with some shortness of breath.

O: *Vital Signs:* T 99.2^F P 106 R 26 B/P 110/68 Pulse O_2 97 percent.
Skin: Pallor present. Erythematous maculopapular rash on face.
Neuro: Cranial nerves ii–xii intact.
HEENT: WNL. No lymphadenopathy.
Respiratory: Clear to auscultation bilaterally.
Cardiac: S1 S2 with a grade-ii systolic murmur at the left sternal border.
Abdomen: Soft; non-tender. No organomegaly.
GU: Deferred.
Musculoskeletal: Slight swelling of the wrist and hands. Slightly painful to palpation.
Rectal: Stool for occult blood was negative.

A: Severe anemia of undetermined origin. AIDS.

P: Discontinue antiretroviral regimen because Combivir has a zidovudine component that can suppress the bone marrow.

- Admit to hospital for acute treatment of severe anemia.
- Transfuse 3 units packed red blood cells.
- Simultaneously start on epoetin alpha 40,000 units subcutaneously weekly to help increase the hemoglobin and prevent additional blood transfusions.
- Repeat hemoglobin post transfusion – 24 percent.
- Transfuse an additional 2 units of packed red blood cells.
- Repeat hemoglobin post second transfusion – 22 percent.

Additional labs ordered at this time were done to widen the clinical search for the underlying cause of the patient's unresolving anemia. In addition to the serology, an endoscopy was performed to rule out an occult bleed. No bleeding was found.

Revised Diagnosis and Treatment Plan

- Parvovirus B19 titer – IgM antibody positive.
- Severe anemia related to B19 parvovirus infection.
- Maintain epoetin alpha 40,000 units SC weekly. Increase to 60,000 units weekly at week 4 if hemoglobin increase is less than 1 g/dL.
- Give IV immune globulin 2 gms per kg of body weight times one dose to treat the parvovirus infection.
- Weekly CBC until hemoglobin is stable.
- Restart antiretroviral therapy consisting of stavudine (Zerit®) 40 mg BID, lamivudine (Epivir®) 150 mg BID, and nelfinavir mesylate (Viracept®) five 250 mg tablets BID when stable.

Key Learning Points

1. Infection with parvovirus B19 is usually benign in children and adults with intact immune systems. In childhood, this viral exanthem is known as Fifth Disease with the classic "slapped cheek" rash.
2. Transmission is believed to be by droplets with a 50 percent contagion rate in households. The patient's partner and child should be assessed for any symptoms.
3. Severe anemia in HIV disease should be closely and carefully monitored. Complete blood counts should be done at least weekly and as directed by symptoms.

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DRUG	INDICATION	DOSE
Aranesp® (darbepoetin alfa) Amgen Patient Support: www.aranesp.com | 1-800-272-9376	For the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy.	The recommended starting dose for Aranesp is 2.25 mcg/kg administered as a weekly SC injection. Dose adjustment of 4.5 mcg/kg should be done if there is not an increase of 1.0 g/dL in the hemoglobin within the first 6 weeks. Dose titration should not exceed a hemoglobin level of 12 g/dL. If the hemoglobin exceeds 12 g/dL, the dose should be reduced by approximately 25%. If the hemoglobin exceeds 13 g/dL, doses should be temporarily withheld until the hemoglobin falls to 12 g/dL. At this point, therapy should be reinitiated at a dose approximately 25% below the previous dose.
Procrit® (epoetin alfa) Ortho Biotech Patient Support: www.procrit.com | 1-800-553-3851	Anemia (low red blood count)	40,000 units subcutaneously weekly* * Dose is investigational

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Stress Reduction and HIV

JUDY K SHAW, MS, ACRN, FNP

Stress has become a buzzword in our daily lives. People talk about stress related to work, finances, relationships, medical problems, etc. Hardly a day goes by that we do not discuss the effect of stress in someone's life, either pointedly or inferred. There are always deadlines or goals that must be met, and with the pace of life today, each causes a pressure that can affect us more than we may realize.

Hans Seyle is considered the father of stress theory and research. He proposed that stress is an innate physiological reaction to real or perceived danger.[1] This reaction is typically referred to as the "fight or flight" response. When confronted with stimuli that we feel is overwhelming or dangerous, our bodies react automatically: heart rate increases, blood is shunted to skeletal muscle to enhance our ability to run or escape, a rise in blood sugar ensures an adequate energy source for muscles, pupils dilate to increase visual acuity, and breathing rates increase to raise the amount of oxygen available to our organs. Other less desirable responses may also occur including irregular heart rhythm, increase in gastric acid, suppression of the immune system, fat storage, agitation, and suppression of sex hormones.[2] Over extended periods of time, these conditions can impair our functioning and cause illness.

Seyle theorized that people did not have control over these responses but rather automatically adapted to the stimuli found in their environment. Later theorists did not agree with his assumptions. They felt that people could learn how to cope effectively with stress, minimize their physiological response, and therefore reduce symptoms and improve their quality of life.[3,4]

Numerous studies have been conducted examining the effect of stress reduction and relaxation. Castillo-Richmond et al. looked at the effect of stress reduction using Transcendental Meditation on atherosclerosis in a group of hypertensive African Americans.[5] Outcome was determined by serial measurements of the carotid intima-media thickness (IMT), a surrogate measure of coronary atherosclerosis and a recognized predictor of stroke. Results indicated that over a 6- to 9-month period, there was a significant change in IMT in the TM group (decrease) compared to the health education group (increase) ($p = 0.038$).

In other studies, relaxation techniques have had a positive effect on weight gain, oxygen consumption, inflammatory response, mood disturbances, anxiety, and other symptoms of stress.[6–10]

In addition to the causes of stress mentioned above, it has long been recognized that an alteration in health status, especially chronic illness, can cause stress for individuals and their family members and/or significant others. As the affected person makes the transition from the role of caregiver to care needer, from being independent to dependent, and from being future-oriented to being uncertain about the future, coping skills are challenged.

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TABLE 1. Simple Stress-Reduction Techniques and Outcomes

Intervention	Action	Outcome
Anger management	Gain control by: • Taking a break from the situation • Deep breathing • Purposely considering all options	Anger level is decreased.
Affirmations	Decrease negative energy by: • Confirming a state of peace • Focusing on relaxing thoughts • Repeating positive mantras	Mind is centered on positive thoughts.
Imagery	Remember peaceful past experiences or create new ones: • Walk along the ocean shore • Sit in the forest • Relax in a tub of hot water	Peaceful experiences are recalled from the past or new mental images are created.
Breathing awareness	Take deep, purposeful breaths in a steady rhythm.	The sympathetic nervous system returns to normal functioning.
Conflict resolution	Promote understanding by: • Developing problem-solving skills • Communicating openly • Identifying problems • Considering options	Conflict resolution and effective communication.
Exercise	Promotes endorphin release to enhance sense of well-being: • Walks •Skating •Dancing • Biking •Yoga	Relaxation
Mental relaxation	Escape from stressful conditions by: • Reading a good book or magazine • Listening to music • Enjoying time with family or friends • Relaxing with a pet • Helping someone in need • Prayer and/or meditating	Allows time for renewal and refreshing.

DRUG	STANDARD DAILY DOSING	POTENTIAL SIDE EFFECTS/OTHER CONSIDERATIONS
Celexa® (citalopram hydrobromide) Forest Pharmaceuticals Patient Support: www.celexa.com | 800 851-0785	20 mg tablet 1-2 times daily	Use of MAOIs and tricyclic antidepressants is contraindicated. Side effects may include nausea, sexual dysfunction, dry mouth, insomnia, weight gain or loss, and dizziness.
Effexor® (venlafaxine hydrochloride) Wyeth Pharmaceuticals Patient Support: www.effexor.com | 800 934-5556	75 mg tablet 1-3 times daily	Use of MAOIs is contraindicated. Persons with liver disease or renal disease should consult with a doctor before using. Side effects may include nausea, insomnia, nervousness, weight loss, dizziness, and sexual dysfunction.
Paxil® (paroxetine hydrochloride) GlaxoSmithKline Patient Support: www.paxil.com | 888 825-5249	20 mg tablet 1-2 times daily	Use of MAOIs and tricyclic antidepressants is contraindicated. Side effects may include nausea, somnolence, insomnia, sexual dysfunction, decreased appetite, headache, and nervousness.
Wellbutrin® (buproprion hydrochloride) GlaxoSmithKline Patient Support: www.wellbutrin.com | 888.825.5249	200 mg tablet 1-2 times daily	Use of MAOIs is contraindicated. Persons taking the protease inhibitors Norvir or Kaletra should consult with a doctor before taking this drug. Side effects may include insomnia, decreased appetite, and shakiness.
Zoloft® (sertraline hydrochloride) Pfizer Patient Support: www.zoloft.com | 800.840.5407	50 mg tablet 1-4 times daily	Persons with liver disease should not take this medication. Use of MAOIs is also contraindicated. Side effects may include nausea, dry mouth, and sexual dysfunction.

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Assessment of Cognitive Changes in HIV/AIDS

JEANNE K. KEMPPAINEN, PHD, RN, CNS

Since the introduction of highly active antiretroviral therapies (HAART), the incidence of HIV dementia has been decreasing in persons with high levels of adherence to these therapies. Despite recent advances in treatment, however, HIV-associated cognitive impairment remains an important focus of clinical care and treatment.

An estimated 30 percent of persons diagnosed with HIV/AIDS will develop cognitive changes, and an additional 15 to 20 percent will develop more profound, debilitating dementia.[1] HIV-associated dementia is now one of the leading causes of dementia in young Americans, and the proportion of new cases in persons with CD4 counts in the higher ranges of 201 mm^3 to 350 mm^3 appears to be increasing.[2]

Prompt recognition and treatment are important for several reasons. First, early diagnosis of cognitive changes may influence decisions about medications and the overall course of treatment. Second, early treatment can play an essential role in diminishing the overall impact of dementia on the quality of life in persons with HIV/AIDS, and can also improve the overall sense of well-being.

Cognitive changes associated with HIV disease vary in severity from mild neurocognitive changes to more profound, disabling dementia. The main distinguishing factor between the two levels of involvement is the person's ability to manage day-to-day activities.[3] Mild neurocognitive changes associated with HIV disease generally do not create major disruptions in life functioning. An important concern, however, is that these changes can still affect a person's ability to comply with complex HIV medication regimens and other treatments. The more severe dementia that occurs primarily in the late stages of HIV disease results in major disruptions in work, home life, and in the ability to perform normal activities of daily living. The progression of cognitive changes can be quite variable because mild neurocognitive changes may or may not progress to more severe forms of dementia. While some persons experience a more "typical" cognitive decline over a period of 3–6 months, others with mild involvement remain cognitively stable throughout the course of HIV disease.

A practical approach to evaluation of HIV dementia requires the recognition of early cognitive and functional changes. The first noticeable symptoms typically include problems with concentration and attention.[1] For example, persons may complain that they lose track of conversations, or they report difficulty in tracking the plots of books or films. Keeping up with everyday tasks, finances, or business issues may also overwhelm them. They may report fatigue when engaging in tasks that require prolonged mental concentration, or they may have difficulty remembering telephone numbers, appointments, or maintaining medication schedules. Motor complaints, such as poor handwriting, an unsteady balance or gait, and a tendency to drop things easily, are frequently early symptoms of cognitive impairment.[1] Friends and partners may also report mood disturbances, changes in personality, apathy, or social withdrawal.

Persons with advancing HIV dementia experience more profound and generalized signs and symptoms including:

- Severe forgetfulness
- Difficulty with concentration
- Problems naming and finding words
- Marked mental slowness
- Disorientation
- Increased apathy
- Problems managing independent living
- Severe motor retardation

Because the HIV virus affects subcortical brain structures, many higher mental functions originating in the cortical sections of the brain remain intact. Unlike persons with Alzheimer's disease, persons in the early stages of HIV/AIDS dementia may not have difficulty understanding spoken or written communication. Initially, the ability to do math calculations or maintain language is usually not affected. The general slowing in thought and psychomotor speed is also more characteristic of subcortical dementia.

Screening tests for cognitive loss can be of great value in identifying those for whom further neuropsychiatric testing could be helpful. Screening is currently recommended for persons with CD4 counts of 200 mm^3 or less.[1] Because cognitive changes associated with HIV/AIDS affect different brain structures than other disorders do, most dementia-screening instruments are not effective in identifying early cognitive changes. One of the most useful tests is a modification of the Mini Mental Status Exam, The HIV Dementia Scale. This test was developed and validated by Power and colleagues.[1,4] The screening instrument consists of four questions that target motor speed, concentration, and memory. The HIV Dementia Scale takes about 10 minutes to administer and has the important advantage of being extremely easy to use.

Because early symptoms of HIV dementia are often subtle, they may easily be overlooked or confused with other medical or psychiatric disorders. Noticeable changes in mental status or function require careful consideration of other factors that can potentially affect concentration, or the ability to process information, such as:

- Anxiety and depression
- Medication side effects
- Metabolic encephalopathy
- Vitamin B_{12} deficiency
- Recreational drugs
- Drug interactions with protease inhibitors
- Sensory loss
- Fatigue

For example, complaints of depression and anxiety are frequent among persons with HIV/AIDS, especially during the latter stages of infection. Persons with major depression frequently report "feeling slowed down" and also have difficulty concentrating. Increasing apathy, social withdrawal, and mental slowing are frequently mistaken for depressive symptoms. Cognitive changes related to nutritional deficiencies, such as Vitamin B_{12} deficiency, may also be confused with cognitive impairments due to HIV infection.[5] Vitamin B_{12} deficiency is associated with significant slowing of information processing. The social use of alcohol and/or other recreational substances may have a significant impact on cognitive function, especially in the area of attention and speed of information processing.[6] HIV disease can also be accompanied by painful neuropathies, myopathies, or other painful opportunistic infections that can distract a person's ability to attend to complex tasks. Sensory losses, including touch sensation or visual impairments, can also impact information processing.[5]

When cognitive changes are recognized, referrals for more thorough medical or neuropsychiatric evaluation are warranted.

Recognizing cognitive changes will become more essential as new treatment approaches become available. Providers can play a valuable role in identifying persons who will benefit from the newer treatments so that optimum quality of life can be maintained.

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Lipids and Cardiovascular Risk in HIV/AIDS

BILL VALENTI, MD

Protease inhibitors (PIs) are associated with metabolic abnormalities that may increase risk of cardiovascular disease; these abnormalities include lipid abnormalities, insulin resistance, and fat redistribution. Although abnormal lipid metabolism in patients with HIV was described before the advent of highly active antiretroviral therapy (HAART), it is more common and more severe with some PI therapies.[1] HAART-associated hyperlipidemia is characterized by increased levels of total cholesterol, with most of the increase in very-low-density lipoprotein cholesterol (VLDL-C) and intermediate-density lipoprotein cholesterol (IDL-C).[1–3] Hypertriglyceridemia is also seen and may be particularly severe in patients taking certain PIs, such as ritonavir. (See the discussion about Protease Inhibitors in the Pipeline elsewhere in this issue.)

Ongoing studies are investigating the association between these medications and cardiovascular disease. Until the risk associated with PIs is better understood, identifying patients at potential high risk for adverse cardiovascular events such as heart attacks, cardiac death, and stroke is an important priority for patients and providers.

The standard approach to coronary risk assessment begins with determining levels of cardiac risk factors. The more severe the abnormality of the risk factor, the higher the risk of a coronary event. Similarly, more risk factors increase vascular risk.

National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III Guidelines

In the NCEP ATP III guidelines, the first step in risk assessment is to count the number of risk factors that modify low-density lipoprotein cholesterol (LDL-C).[4] When two or more risk factors are observed in any given patient, the long-term Framingham Study is used to further estimate the 10-year risk of myocardial infarction or cardiac death more accurately. These risk assessment tools are available online at: www.nhlbi.nih.gov/guidelines/cholesterol/index.htm.

After determining the appropriate risk category, LDL-C goals are identified.[4] The primary aim of therapy for most patients is to normalize LDL-C. An LDL-C level less than 100 mg/dL is optimal, although it is not necessarily the target nor is it easily achieved for every patient.

In the NCEP ATP III guidelines, a high-density lipoprotein cholesterol (HDL-C) level <40 mg/dL is considered "low." A triglyceride level <150 mg/dL is defined as "normal," and a level ≥200 mg/dL is defined as "high." If severe hypertriglyceridemia (≥500 mg/dL) is present, reduction of the triglyceride level becomes the primary target.

Guidelines from the International AIDS Society

Recently, a panel of the International AIDS Society–USA (IAS–USA) published recommendations on the management of metabolic complications associated with antiretroviral therapy.[5] This international, multidisciplinary panel reviewed available data published or presented from 1997 to 2002. Extrapolation from preliminary results of ongoing studies and experience garnered from management of similar metabolic abnormalities in patients without HIV-1 infection also serve as the basis for many of these recommendations.

The remainder of this discussion is limited only to IAS recommendations on management of lipid disorders associated with HAART.

- *Glucose and lipid abnormalities.* Before the initiation of HAART, 3 to 6 months after starting or switching therapy, and at least annually during therapy, assess fasting glucose if therapy includes a PI and fasting lipid panel (i.e., total cholesterol, HDL and LDL cholesterol, and triglyceride levels).
- *Lipid and lipoprotein abnormalities.* Follow NCEP III guidelines for assessment of risk factors for cardiovascular disease, and initiate dietary and lifestyle alterations to lower cholesterol and triglyceride levels.
- *Treatment strategies.* Avoid PI use, if possible, in patients with preexisting cardiovascular risk factors, a family history of hyperlipidemia, or elevated lipid levels. Follow NCEP guideline thresholds for lipid-lowering therapy. Fibrates are recommended as initial therapy for those with isolated fasting hypertriglyceridemia. Pravastatin or atorvastatin are preferred statin agents for those with isolated fasting hypercholesterolemia requiring treatment in the setting of PI or other CYP3A4 inhibitor therapy. If combination therapy for hypercholesterolemia and hypertriglyceridemia is indicated, therapy should begin with a statin, followed by the addition of a fibrate if there is insufficient response after 3 to 4 months of treatment.

Conclusions: Implications for Patient Care

In summary, the NCEP III and IAS-USA conclude that:

- High-risk individuals with CAD or a "coronary risk equivalent" should be identified and should be offered such treatment as is required to achieve their LDL and non-HDL cholesterol targets.
- Therapeutic lifestyle changes should be initiated for all individuals with lipid levels above their targets. Lipid-lowering agents can be initiated simultaneously with lifestyle changes (e.g., smoking cessation, diet modifications, and exercise) in patients with CAD or a coronary risk equivalent, or in those who have more than two risk factors and a 10-year risk >10 percent.
- Choice of lipid-altering therapy is a complex matter and is not well studied in HIV. Switching to a different PI or to PI-sparing regimens are other options.

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Ocular CMV: A Review

JUDY K SHAW, MS, ACRN, FNP

Cytomegala Virus (CMV) retinitis occurred in up to 40 percent of patients with advanced AIDS before the introduction of Highly Active Antiretroviral Therapy (HAART); in the era of HAART, the incidence has decreased more than 50 percent.[1] Without treatment, CMV lesions enlarge and develop necrosis and edema of all the layers of the retina, eventually progressing to atrophic scar tissue. Affected tissue is unable to regenerate, and vision is permanently impaired. The goal of treatment is to prevent further necrosis and loss of vision. Some improvement may be seen on an effective regimen of HAART alone, and it is considered safe to stop maintenance anti-CMV therapy following immune recovery when the CD4 count is stable and is greater than 100 mm–150 mm for 3 months.[1,2] This decision should be made only after considering the extent of immune recovery and the degree of vision loss.[3]

However, there are reports that immune recovery may lead to negative ophthalmic complications in some cases, including uveitis, vitritis, macular and disc edema, and cataract.[4] The etiology of this phenomenon is not yet clearly understood.

The most common symptom suggesting CMV retinitis is altered vision resulting from floaters, flashing lights, or "cotton spots" depending on the anatomic location of retinal damage. The Amsler Grid is a quick and effective screening tool that can be used easily in the clinical setting; it may also be distributed for self-monitoring.

There is a positive result when there is a disruption of the grid lines or an appearance of "cotton spots" within the field of vision on the grid. In the absence of an Amsler Grid, a newspaper can be placed on the floor. There is a positive result when there is a report of missing print or "cotton spots" obscuring the print rather than an inability to read the material.

On examination, retinal lesions with exudate and hemorrhages are diagnostic of CMV infection. The development of ocular disease poses a serious threat to people with severe immunosuppression.

The CD4 count has been identified as the best predictor of a person's ability to initiate an effective immune response to CMV, even more so than the HIV viral load. CD4 counts less than 50 have been associated with a greater likelihood of infection.[4]

The current treatments have not changed dramatically in the past five years and can be found in Table 1. These are based on recommendations from the International AIDS Society[6] and are adapted from 2000-2001 Medical Management of HIV Infection.[3]

Possible side effects with CMV treatment include the following:

- Ganciclovir: neutropenia, thrombocytopenia
- Foscarnet: renal failure, electrolyte imbalance
- Cidofovir: renal failure
- Fomivirsen: lack of systemic protection
- Valganciclovir: granulocytopenia or neutropenia, anemia, and thrombocytopenia.

Also,Valganciclovir has been known to cause birth defects. Effective contraception should be used during dosing and for at least 90 days following treatment with Valganciclovir. For women this means using barrier protection (condoms) and one additional form of contraception (birth control pills, intrauterine device). For men this means using barrier protection (condoms).

IV gancyclovir and foscarnet, or a combination of both medications, are used for treatment in cases involving the GI, pulmonary, or CNS system. Side effects are similar to those mentioned above.

Valganciclovir (Valcyte®, Roche), a prodrug of ganciclovir, is an oral agent that has been developed for treatment of CMV retinitis in people with AIDS. An oral dose of 900 mg of valganciclovir is comparable to a dose of 5 mg/kg of IV ganciclovir (Cytovene®, Roche). Studies have demonstrated that this agent has produced equally effective results in the treatment groups using these medications.[6] Similar side effects have been reported including neutropenia, thrombocytopenia, GI distress (nausea, vomiting, diarrhea), fever, headache, insomnia, peripheral neuropathy, and retinal detachment.

Prevention of CMV by early diagnosis of HIV, effective antiretroviral therapy, and regular screening is the best way to avoid complications of this and other opportunistic infections.

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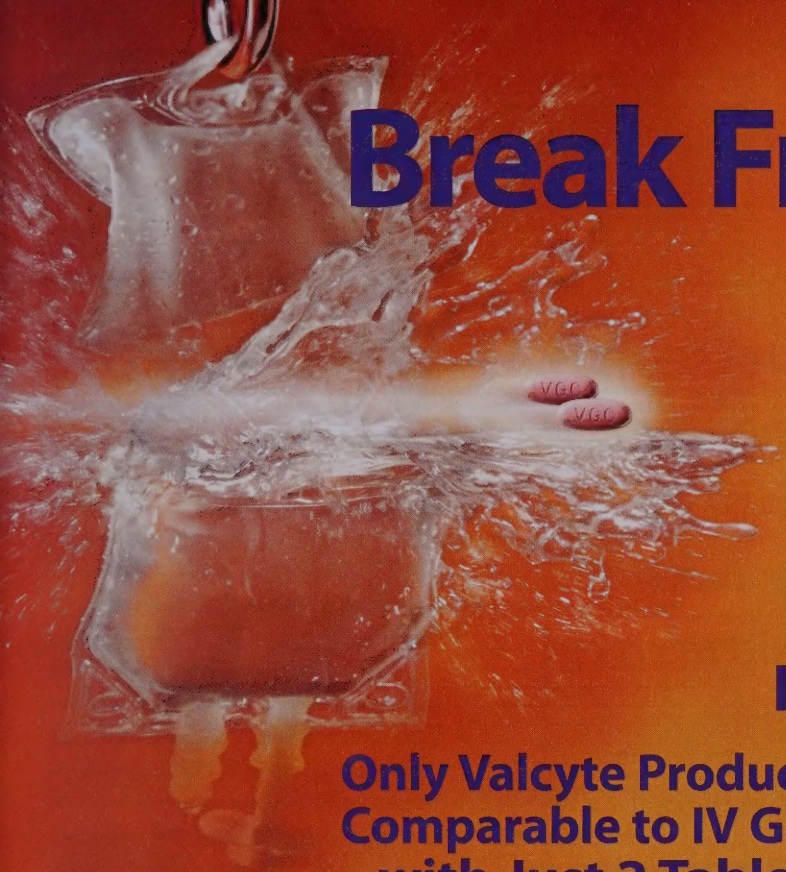
CMV Treatment Update

A study published recently in the New England Journal of Medicine *has demonstrated that orally administered valganciclovir (Valcyte®, Roche) is as effective as intravenous (IV) dosing for induction treatment of CMV retinitis. People living with AIDS and those with newly diagnosed CMV retinitis were given valganciclovir 900 mg twice daily and were compared to a group who received standard IV ganciclovir induction. The primary endpoint was the progression to photographically determined CMV retinitis within 4 weeks after drug induction. For the IV agent, the median number of days to progression was 125 for development of retinitis; for oral valgancicilovir, it was 160 days. Oral administration appears to be as effective as intravenous dosing and is much more convenient.*

Source: Martin DF, Sierra-Madero J, Walmsley S, et al. A controlled trial of valganciclovir as induction treatment for cytomegalovirus retinitis. New Engl J Med. 2003;346:1119–1126.



Break Free from IV...

Convenient CMV Therapy

Valcyte™

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IV Potency. Oral Delivery.

Only Valcyte Produces Ganciclovir Blood Levels Comparable to IV Ganciclovir as Measured by AUC ...with Just 2 Tablets[1]

Induction Therapy	Maintenance Therapy
2 Valcyte 450-mg tablets **twice daily** with food for 21 days	2 Valcyte 450-mg tablets **once daily** with food

- **Strict adherence to dosage recommendations is essential to avoid overdose**
  - **Ganciclovir bioavailability from Valcyte tablets is significantly higher than from ganciclovir capsules; therefore, Valcyte tablets cannot be substituted for ganciclovir capsules on a 1-to-1 basis**
- **Dosage reductions, based on creatinine clearance, are required for Valcyte tablets in patients with renal impairment**

Valcyte tablets are indicated for the treatment of cytomegalovirus (CMV) retinitis in people living with acquired immunodeficiency syndrome (AIDS).

The clinical toxicity of Valcyte, which is metabolized to ganciclovir, includes granulocytopenia, anemia and thrombocytopenia. In animal studies ganciclovir was carcinogenic, teratogenic and caused aspermatogenesis. Valcyte should not be administered if the absolute neutrophil count is less than 500 cells/µL, the platelet count is less than 25,000/µL or the hemoglobin is less than 8 g/dL. Didanosine blood levels can be significantly increased when didanosine is taken with Valcyte. Cytopenias may be exacerbated by zidovudine. Other side effects occurring with a frequency of ≥5% may include diarrhea, fever, nausea, neutropenia, headache, vomiting, insomnia, abdominal pain, retinal detachment, peripheral neuropathy and paresthesia.

Reference: 1. Data on file (Ref. 156-003), Hoffmann-La Roche Inc., Nutley, NJ 07110.

Please see brief summary of product information, which includes contraindications, warnings, precautions and adverse events, on following page.

Roche Pharmaceuticals

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17-090-018-014-0302

Before prescribing, please see complete product information, a summary of which follows:

WARNING:

THE CLINICAL TOXICITY OF VALCYTE, WHICH IS METABOLIZED TO GANCICLOVIR, INCLUDES GRANULOCYTOPENIA, ANEMIA AND THROMBOCYTOPENIA. IN ANIMAL STUDIES GANCICLOVIR WAS CARCINOGENIC, TERATOGENIC AND CAUSED ASPERMATOGENESIS.

CONTRAINDICATIONS: Valcyte tablets are contraindicated in patients with hypersensitivity to valganciclovir or ganciclovir.

WARNINGS: Hematologic: Valcyte tablets should not be administered if the absolute neutrophil count is less than 500 cells/µL, the platelet count is less than 25,000/µL, or the hemoglobin is less than 8 g/dL. Severe leukopenia, neutropenia, anemia, thrombocytopenia, pancytopenia, bone marrow depression and aplastic anemia have been observed in patients treated with Valcyte tablets (and ganciclovir) (see PRECAUTIONS: Laboratory Testing and ADVERSE EVENTS in complete product information). Valcyte tablets should, therefore, be used with caution in patients with pre-existing cytopenias, or who have received or are receiving myelosuppressive drugs or irradiation. Cytopenia may occur at any time during treatment and may increase with continued dosing. Cell counts usually begin to recover within 3 to 7 days of discontinuing drug.

Impairment of Fertility: Animal data indicate that administration of ganciclovir causes inhibition of spermatogenesis and subsequent infertility. These effects were reversible at lower doses and irreversible at higher doses (see PRECAUTIONS: Carcinogenesis, Mutagenesis and Impairment of Fertility). It is considered probable that in humans, valganciclovir at the recommended doses may cause temporary or permanent inhibition of spermatogenesis. Animal data also indicate that suppression of fertility in females may occur.

Teratogenesis, Carcinogenesis and Mutagenesis: Because of the mutagenic and teratogenic potential of ganciclovir, women of childbearing potential should be advised to use effective contraception during treatment. Similarly, men should be advised to practice barrier contraception during, and for at least 90 days following, treatment with Valcyte tablets (see PRECAUTIONS: Carcinogenesis, Mutagenesis and Impairment of Fertility and Pregnancy: Category C). In animal studies, ganciclovir was found to be mutagenic and carcinogenic. Valganciclovir should, therefore, be considered a potential teratogen and carcinogen in humans with the potential to cause birth defects and cancers (see DOSAGE AND ADMINISTRATION: Handling and Disposal in complete product information).

PRECAUTIONS: General: Strict adherence to dosage recommendations is essential to avoid overdose. The bioavailability of ganciclovir from Valcyte tablets is significantly higher than from ganciclovir capsules. Patients switching from ganciclovir capsules should be advised of the risk of overdosage if they take more than the prescribed number of Valcyte tablets. **Valcyte tablets cannot be substituted for cytovene capsules on a one-to-one basis** (see OVERDOSAGE and DOSAGE AND ADMINISTRATION in complete product information). Since ganciclovir is excreted by the kidneys, normal clearance depends on adequate renal function. **IF RENAL FUNCTION IS IMPAIRED, DOSAGE ADJUSTMENTS ARE REQUIRED FOR VALCYTE TABLETS.** Such adjustments should be based on measured or estimated creatinine clearance values (see DOSAGE AND ADMINISTRATION: Renal Impairment in complete product information). For patients on hemodialysis (CrCl <10 mL/min) it is recommended that ganciclovir be used (in accordance with the dose-reduction algorithm cited in the approved Cytovene®-IV and Cytovene® Package Insert section on DOSAGE AND ADMINISTRATION: Renal Impairment in complete product information) rather than Valcyte tablets (see DOSAGE AND ADMINISTRATION: Hemodialysis and CLINICAL PHARMACOLOGY: Special Populations: *Hemodialysis* in complete product information).

Laboratory Testing: Due to the frequency of neutropenia, anemia and thrombocytopenia in patients receiving Valcyte tablets (see ADVERSE EVENTS), it is recommended that complete blood counts and platelet counts be performed frequently, especially in patients in whom ganciclovir or other nucleoside analogues have previously resulted in leukopenia, or in whom neutrophil counts are less than 1000 cells/µL at the beginning of treatment. Increased monitoring for cytopenias may be warranted if therapy with oral ganciclovir is changed to oral valganciclovir, because of increased plasma concentrations of ganciclovir after valganciclovir administration (see CLINICAL PHARMACOLOGY in complete product information). Increased serum creatinine levels have been observed in trials evaluating Valcyte tablets. Patients should have serum creatinine or creatinine clearance values monitored carefully to allow for dosage adjustments in renally impaired patients (see DOSAGE AND ADMINISTRATION: Renal Impairment in complete product information). The mechanism of impairment of renal function is not known.

Drug Interactions: Drug Interaction Studies Conducted with Valganciclovir: No in vivo drug-drug interaction studies were conducted with valganciclovir. However, because valganciclovir is rapidly and extensively converted to ganciclovir, interactions associated with ganciclovir will be expected for Valcyte tablets. Drug Interaction Studies Conducted With Ganciclovir: Binding of ganciclovir to plasma proteins is only about 1% to 2%, and drug interactions involving binding site displacement are not anticipated. Drug-drug interaction studies were conducted in patients with normal renal function. Patients with impaired renal function may have increased concentrations of ganciclovir and the coadministered drug following concomitant administration of Valcyte tablets and drugs excreted by the same pathway as ganciclovir. Therefore, these patients should be closely monitored for toxicity of ganciclovir and the coadministered drug.

Table 1. Results of Drug Interaction Studies With Ganciclovir: Effects of Co-administered Drug on Ganciclovir Plasma AUC and C_{max} Values

Co-administered Drug	Ganciclovir Dosage	n	Ganciclovir Pharmacokinetic (PK) Parameter	Clinical Comment
Zidovudine 100 mg every 4 hours	1000 mg every 8 hrs	12	AUC ↓ 17 ± 25% (range: -52% to 23%)	Zidovudine and Valcyte each have the potential to cause neutropenia and anemia. Some patients may not tolerate concomitant therapy at full dosage.
Didanosine 200 mg every 12 hours administered 2 hours before ganciclovir	1000 mg every 8 hrs	12	AUC ↓ 21 ± 17% (range: -44% to 5%)	Effect not likely to be clinically significant.
Didanosine 200 mg every 12 hours simultaneously administered with ganciclovir	1000 mg every 8 hrs	12	No effect on ganciclovir PK parameters observed	No effect expected.
	IV ganciclovir 5 mg/kg twice daily	11	No effect on ganciclovir PK parameters observed	No effect expected.
	IV ganciclovir 5 mg/kg once daily	11	No effect on ganciclovir PK parameters observed	No effect expected.
Probenecid 500 mg every 6 hours	1000 mg every 8 hours	10	AUC ↑ 53 ± 91% (range: -14% to 299%) Ganciclovir renal clearance ↓ 22 ± 20% (range: -54% to -4%)	Patients taking probenecid and Valcyte should be monitored for evidence ofganciclovir toxicity.
Zalcitabine 0.75 mg every 8 hours administered 2 hours before ganciclovir	1000 mg every 8 hours	10	AUC ↑ 13%	Effect not likely to be clinically significant.
Trimethoprim 200 mg once daily	1000 mg every 8 hours	12	Ganciclovir renal clearance ↓ 16.3% Half-life ↑ 15%	Effect not likely to be clinically significant.
Mycophenolate mofetil 1.5 g single dose	IV ganciclovir 5 mg/kg single dose	12	No effect on ganciclovir PK parameters observed (patients with normal renal function)	Patients with renal impairment should be monitored carefully, as levels of metabolites of both drugs may increase.

Table 2. Results of Drug Interaction Studies With Ganciclovir: Effects of Ganciclovir on Plasma AUC and C_{max} Values of Co-administered Drug

Co-administered Drug	Ganciclovir Dosage	n	Co-administered Drug Pharmacokinetic (PK) Parameter	Clinical Comment
Zidovudine 100 mg every 4 hours	1000 mg every 8 hrs	12	AUC_{0-t} ↑ 19 ± 27% (range: -11% to 74%)	Zidovudine and Valcyte each have the potential to cause neutropenia and anemia. Some patients may not tolerate concomitant therapy at full dosage.
Didanosine 200 mg every 12 hours when administered 2 hours prior to or concurrent with ganciclovir	1000 mg every 8 hrs	12	AUC_{0-12} ↑ 111 ± 114% (range: 10% to 493%)	Patients should be closely monitored for didanosine toxicity.
Didanosine 200 mg every 12 hours	IV ganciclovir 5 mg/kg twice daily	11	AUC_{0-12} ↑ 70 ± 40% (range: 3% to 121%) C_{max} ↑ 49 ± 48% (range: -28% to 125%)	Patients should be closely monitored for didanosine toxicity.
Didanosine 200 mg every 12 hours	IV ganciclovir 5 mg/kg once daily	11	AUC_{0-12} ↑ 50 ± 26% (range: 22% to 110%) C_{max} ↑ 36 ± 36% (range: -27% to 94%)	Patients should be closely monitored for didanosine toxicity.
Zalcitabine 0.75 mg every 8 hours administered 2 hours before ganciclovir	1000 mg every 8 hours	10	No clinically relevant PK parameter changes	No effect expected.
Trimethoprim 200 mg once daily	1000 mg every 8 hours	12	Increase in C_{min}	Effect not likely to be clinically significant.
Mycophenolate mofetil 1.5 g single dose	IV ganciclovir 5 mg/kg single dose	12	No PK interaction observed (patients with normal renal function)	Patients with renal impairment should bemonitored carefully, as levels of metabolites of both drugs may increase.

Carcinogenesis, Mutagenesis and Impairment of Fertility[‡]: No long-term carcinogenicity studies have been conducted with valganciclovir. However, upon oral administration, valganciclovir is rapidly and extensively converted to ganciclovir. Therefore, like ganciclovir, valganciclovir is a potential carcinogen. Ganciclovir was carcinogenic in the mouse at oral doses of 20 and 1000 mg/kg/day (approximately 0.1x and 1.4x, respectively, the mean drug exposure in humans following the recommended intravenous dose of 5 mg/kg, based on area under the plasma concentration curve [AUC] comparisons). At the dose of 1000 mg/kg/day there was a significant increase in the incidence of tumors of the preputial gland in males, forestomach (nonglandular mucosa) in males and females and reproductive tissues (ovaries, uterus, mammary gland, clitoral gland and vagina) and liver in females. At the dose of 20 mg/kg/day, a slightly increased incidence of tumors was noted in the preputial and harderian glands in males, forestomach in males and females and liver in females. No carcinogenic effect was observed in mice administered ganciclovir at 1 mg/kg/day (estimated as 0.01x the human dose based on AUC comparison). Ganciclovir should be considered a potential carcinogen in humans. Valganciclovir increases mutations in mouse lymphoma cells. In the mouse micronucleus assay, valganciclovir was clastogenic at a dose of 1500 mg/kg (60x human mean exposure for ganciclovir based upon AUC). Valganciclovir was not mutagenic in the Ames Salmonella assay. Ganciclovir increased mutations in mouse lymphoma cells and DNA damage in human lymphocytes in vitro. In the mouse micronucleus assay, ganciclovir was clastogenic at doses of 150 and 500 mg/kg (IV) [2.8 to 10x human exposure based on AUC] but not 50 mg/kg (exposure approximately comparable to the human based on AUC). Ganciclovir was not mutagenic in the Ames Salmonella assay. Valganciclovir is converted to ganciclovir and therefore is expected to have similar reproductive toxicity effects as ganciclovir (see WARNINGS: Impairment of Fertility). Ganciclovir caused decreased mating behavior, decreased fertility and an increased incidence of embryolethality in female mice following intravenous doses of 90 mg/kg/day (approximately 1.7x the mean drug exposure in humans following the dose of 5 mg/kg, based on AUC comparisons). Ganciclovir caused decreased fertility in male mice and hypospermatogenesis in mice and dogs following daily oral or intravenous administration of doses ranging from 0.2 to 10 mg/kg. Systemic drug exposure (AUC) at the lowest dose showing toxicity in each species ranged from 0.03 to 0.1x the AUC of the recommended human intravenous dose. Valganciclovir caused similar effects on spermatogenesis in mice, rats and dogs. It is considered likely that ganciclovir (and valganciclovir) could cause inhibition of human spermatogenesis.

Pregnancy: Category C[‡]: Valganciclovir is converted to ganciclovir and therefore is expected to have reproductive toxicity effects similar to ganciclovir. Ganciclovir has been shown to be embryotoxic in rabbits and mice following intravenous administration, and teratogenic in rabbits. Fetal resorptions were present in at least 85% of rabbits and mice administered 60 mg/kg/day and 108 mg/kg/day (2x the human exposure based on AUC comparisons), respectively. Effects observed in rabbits included: fetal growth retardation, embryolethality, teratogenicity and/or maternal toxicity. Teratogenic changes included cleft palate, anophthalmia/microphthalmia, aplastic organs (kidney and pancreas), hydrocephaly and brachygnathia. In mice, effects observed were maternal/fetal toxicity and embryolethality. Daily intravenous doses of 90 mg/kg administered to female mice prior to mating, during gestation and during lactation caused hypoplasia of the testes and seminal vesicles in the month-old male offspring, as well as pathologic changes in the nonglandular region of the stomach (see Teratogenesis, Carcinogenesis and Mutagenesis). The drug exposure in mice as estimated by the AUC was approximately 1.7x the human AUC. Data obtained using an ex vivo human placental model show that ganciclovir crosses the placenta and that simple diffusion is the most likely mechanism of transfer. The transfer was not saturable over a concentration range of 1 to 10 mg/mL and occurred by passive diffusion. Valganciclovir may be teratogenic or embryotoxic at dose levels recommended for human use. There are no adequate and well-controlled studies in pregnant women. Valcyte tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

[‡]Footnote: All dose comparisons presented in the Carcinogenesis, Mutagenesis, and Impairment of Fertility and Pregnancy subsections are based on the human AUC following administration of a single 5 mg/kg infusion of intravenous ganciclovir.

Nursing Mothers: It is not known whether ganciclovir or valganciclovir is excreted in human milk. Because valganciclovir caused granulocytopenia, anemia and thrombocytopenia in clinical trials and ganciclovir was mutagenic and carcinogenic in animal studies, the possibility of serious adverse events from ganciclovir in nursing infants is possible (see WARNINGS in complete product information). Because of potential for serious adverse events in nursing infants, **mothers should be instructed not to breast-feed if they are receiving Valcyte tablets.** In addition, the Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV.

Pediatric Use: Safety and effectiveness of Valcyte tablets in pediatric patients have not been established.

Geriatric Use: The pharmacokinetic characteristics of Valcyte in elderly patients have not been established. Since elderly individuals frequently have a reduced glomerular filtration rate, particular attention should be paid to assessing renal function before and during administration of Valcyte (see DOSAGE AND ADMINISTRATION in complete product information). Clinical studies of Valcyte did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy. Valcyte is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. In addition, renal function should be monitored and dosage adjustments should be made accordingly (see PRECAUTIONS: General, CLINICAL PHARMACOLOGY: Special Populations: *Renal Impairment*, and DOSAGE AND ADMINISTRATION: Renal Impairment in complete product information).

ADVERSE EVENTS: Experience With Valcyte Tablets: Valganciclovir, a pro-drug of ganciclovir, is rapidly converted to ganciclovir after oral administration. Adverse events known to be associated with ganciclovir usage can therefore be expected to occur with Valcyte tablets. As shown in Table 3, the safety profiles of Valcyte tablets and intravenous ganciclovir during 28 days of randomized therapy (21 days induction dose and 7 days maintenance dose) in 158 patients were comparable, with the exception of catheter-related infection, which occurred with greater frequency in patients randomized to receive IV ganciclovir (see Table 3).

Table 3. Percentage of Selected Adverse Events Occurring During the Randomized Phase of Study WV15376

Adverse Event	Valganciclovir Arm n=79	Intravenous Ganciclovir Arm n=79
Diarrhea	16%	10%
Neutropenia	11%	13%
Nausea	8%	14%
Headache	9%	5%
Anemia	8%	8%
Catheter-related infection	3%	11%

Tables 4 and 5 show the pooled adverse event data and abnormal laboratory values from two single-arm, open-label clinical trials, WV15376 (after the initial 4 weeks of randomized therapy) and WV15705). A total of 370 patients received maintenance therapy with valganciclovir tablets 900 mg q day. Approximately 252 (68%) of these patients received Valcyte tablets for more than 9 months (maximum duration was 36 months).

Table 4. Pooled Selected Adverse Events Reported in ≥5% of Patients in Two Clinical Studies

Adverse Events According to Body System	% Patients N=370
Gastrointestinal system	
Diarrhea	41%
Nausea	30%
Vomiting	21%
Abdominal pain	15%
Body as a whole	
Pyrexia	31%
Headache	22%
Hemic and lymphatic system	
Neutropenia	27%
Anemia	26%
Thrombocytopenia	6%
Central and peripheral nervous system	
Insomnia	16%
Peripheral neuropathy	9%
Paresthesia	8%
Special senses	
Retinal detachment	15%

Serious adverse events reported from these two clinical trials (N=370) with a frequency of less than 5% and which are not mentioned in the two tables above are: *Hemic and lymphatic system:* pancytopenia, bone marrow depression, aplastic anemia; *Urogenital system:* decreased creatinine clearance; *Infections:* local and systemic infections and sepsis; *Bleeding complications:* potentially life-threatening bleeding associated with thrombocytopenia; *Central and peripheral nervous system:* convulsion, psychosis, hallucinations, confusion, agitation; *Body as a whole:* valganciclovir hypersensitivity.

Laboratory abnormalities reported with Valcyte tablets are listed below:

Table 5. Pooled Laboratory Abnormalities Reported in Two Clinical Studies

Laboratory Abnormalities	N=370
Neutropenia: ANC/µL	
<500	19%
500 – <750	17%
750 – <1000	17%
Anemia: Hemoglobin g/dL	
<6.5	7%
6.5 – <8.0	13%
8.0 – <9.5	16%
Thrombocytopenia: Platelets/µL	
<25,000	4%
25,000 – <50,000	6%
50,000 – <100,000	22%
Serum Creatinine: mg/dL	
>2.5	3%
>1.5 – 2.5	12%

Experience With Ganciclovir: Valganciclovir is rapidly converted to ganciclovir upon oral administration. Adverse events reported with Valcyte in general were similar to those reported with ganciclovir (Cytovene). Please refer to the Cytovene label for more information on post-marketing adverse events associated with ganciclovir.

OVERDOSAGE: Overdose Experience With Valcyte Tablets: One adult developed fatal bone marrow depression (medullary aplasia) after several days of dosing that was at least 10-fold greater than recommended for the patient's estimated degree of renal impairment. It is expected that an overdose of Valcyte tablets could also possibly result in increased renal toxicity (see PRECAUTIONS: General and DOSAGE AND ADMINISTRATION: Renal Impairment in complete product information). Since ganciclovir is dialyzable, dialysis may be useful in reducing serum concentrations in patients who have received an overdose of Valcyte tablets. Adequate hydration should be maintained. The use of hematopoietic growth factors should be considered (see CLINICAL PHARMACOLOGY: Special Populations: *Hemodialysis* in complete product information).

Overdose Experience With Intravenous Ganciclovir: Reports of overdoses with intravenous ganciclovir have been received from clinical trials and during postmarketing experience. The majority of patients experienced one or more of the following adverse events: *Hematological toxicity:* pancytopenia, bone marrow depression, medullary aplasia, leukopenia, neutropenia, granulocytopenia; *Hepatotoxicity:* hepatitis, liver function disorder; *Renal toxicity:* worsening of hematuria in a patient with pre-existing renal impairment, acute renal failure, elevated creatinine; *Gastrointestinal toxicity:* abdominal pain, diarrhea, vomiting; *Neurotoxicity:* generalized tremor, convulsion.

HOW SUPPLIED: Valcyte (valganciclovir HCl tablets) is available as 450 mg pink convex oval tablets with "VGC" on one side and "450" on the other side. Each tablet contains valganciclovir HCl equivalent to 450 mg valganciclovir. Valcyte is supplied in bottles of 60 tablets (NDC 0004-0038-22). Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP controlled room temperature].

Cytovene is a registered trademark of Syntex (U.S.A.) LLC.

Valcyte tablets are manufactured by Patheon Inc., Mississauga, Ontario, Canada L5N 7K9

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Resistance Testing and Drug Levels: Clinical Applications

BILL VALENTI, MD

Drug selection for failing antiretroviral regimens is always a challenge. Resistance testing is recognized as an important technology when selecting new salvage regimens.[1] In two recently published studies, genotype testing and therapeutic drug monitoring converge with the concept of boosted protease inhibitor (PI) regimens to improve outcomes for patients.[2,3]

The first study by Barreiro, et al. used genotype testing.[2] All patients receiving ritonavir (rit) 100 mg twice daily together with saquinavir (SQV) soft gel 1000 mg twice daily, indinavir (IDV) 800 mg twice daily, or lopinavir (LPV) 400 mg twice daily, as part of a salvage regimen, were retrospectively reviewed. Only subjects who had failed all three antiretroviral drug families in the past were included. A total of 299 patients were included in the study (121 on SQV, 62 on IDV, and 116 on LPV). Mean plasma HIV-RNA and CD4 lymphocyte counts at baseline were less favorable in the LPV group (4.4 logs, 275 cells/mL) with respect to SQV (4.3 logs, 355 cells/mL) and IDV (3.7 logs, 409 cells/mL) groups (PB/0.05).

The proportion of subjects experiencing virological success (either <500 HIV-RNA copies/mL or >1 log reduction) in an intent-to-treat analysis at 24 weeks was 61% with LPV, 49% with SQV and 48% with IDV. The CD4 count increased 48% with SQV, 45% with IDV, and 37% with LPV. The proportion of subjects discontinuing therapy due to adverse events was higher using IDV (27%) than using either SQV (11%) or LPV (6%) (PB/0.05).

The presence of <5 or of 5 or more PI resistance mutations at baseline discriminated significantly better who would respond to therapy in all instances: 90% versus 48% with LPV, 95% versus 21% with SQV, and 90% versus 23% with IDV.

The authors concluded that the efficacy of rit-boosted PI combinations is greatly influenced by the extent of baseline PI resistance. Differences, not only in potency, but mainly in tolerance may favor the selection of one dual PI combination over others.

> Drug selection for failing antiretroviral regimens is always a challenge. Resistance testing is recognized as an important technology when selecting new salvage regimens.

The second study builds on the first, but is prospective and adds drug levels to the equation.[3] A total of 139 HIV-infected adults failing a protease inhibitor (PI) regimen were recruited in a multicenter, prospective, open trial. All began saquinavir soft gel 1000 mg and ritonavir 100 mg twice daily plus two nucleoside analogues. Plasma HIV-RNA levels fell >1 log at 24 weeks in 44.5 percent of patients in an intent-to-treat analysis. The number of PI resistance mutations and saquinavir plasma levels independently predicted the virological response.

The mean plasma HIV-RNA copy number before beginning saquinavir/ritonavir was 4.9 logs. The mean CD4 cell count was 368 cells/mm^3.

With genotype testing, a set of eight codon substitutions at the protease (L10I/R/V, G48V, I54V/L, A71V/T, V77I, V82A, I84V, and L90M) were considered as saquinavir resistance mutations. Blood samples for measuring saquinavir concentrations were collected 12 weeks after beginning treatment and just before the morning dose (to estimate trough concentrations or C_{min}). Trough concentrations of saquinavir <0.1 g/mL were considered to be suboptimal.

In the multivariate analysis, both HIV genotyping and saquinavir levels independently predicted the virological response to saquinavir/ritonavir at 24 weeks. More than 97 percent of patients harboring less than 4 saquinavir resistance mutations together with saquinavir plasma levels > 0.1 µg/mL showed a favorable virological response. In contrast, only 12 percent of subjects with more than 4 saquinavir resistance mutations and suboptimal saquinavir levels showed a satisfactory virological response.

The authors concluded that the data support the integration of both therapeutic drug monitoring and resistance testing in clinical practice, particularly when managing antiretroviral-experienced patients who begin PI-containing regimens. These methods represent useful tools for optimizing therapy and improving outcomes.

See Dr. Valenti's bio on page 11 N

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Use of Resistance Testing in Antiretroviral-Naïve Patients

NICHOLAS S HELLMANN, MD

Drug-resistance tests have become a standard tool for HIV patient management due to the frequent emergence of drug resistance during treatment failure, and the importance of selecting the most effective alternate treatment regimen. However, despite definitive data supporting the use of resistance tests after treatment failure, much uncertainty exists among clinicians regarding the appropriate use of resistance tests in antiretroviral-naïve patients.[1,2] This article will review the rationale and proposed settings for proper use of resistance tests in treatment-naïve patients.

Numerous studies have clearly delineated the increasing prevalence of resistant virus transmission throughout the world, occurring in as many as 10 to 20 percent of newly infected people in North America.[3–5] This fact is likely caused by the increasing use of antiretroviral therapy, and the associated increase in drug resistance. This trend will likely continue as therapy is introduced in all regions of the world. Although early reports have suggested that drug-resistant strains of HIV were not readily transmitted, more recent data demonstrate that even highly resistant viruses are being transmitted.[3–5]

Since the first treatment regimen is the one most likely to produce prolonged clinical benefit, proper initial treatment selection is critical. Due to the increasing prevalence of resistant virus transmission, a strong rationale exists for the use of resistance testing in the newly infected, untreated patient population.[3] Resistance testing will not only help clinicians to select the optimum antiretroviral treatment regimen for immediate use in such patients, but can also help characterize the resistance profile of the infecting virus population for use in selecting a future treatment regimen, if therapy initiation is delayed. Since the infecting virus immediately becomes archived in latently infected cells, and any drug-resistant virus usually disappears over a variable period of time in the absence of therapy, characterization of the patient's drug-resistance profile as close as possible to the time of infection should be a high priority, regardless of the decision to start or delay therapy.

Although the rationale is clear for use of resistance tests in newly infected patients, questions remain regarding the definition of "recently infected" and the duration of persistently detectable drug resistance in such patients. Although drug resistance can disappear within the first 6 to 12 months after infection as the virus mutates to a more fit, drug-sensitive variant, recent data suggest that some drug-resistant viruses can persist for more than a year after primary HIV infection.[6,7] The typical duration of drug resistance after primary infection is the subject of ongoing clinical investigations. Preliminary data suggest that drug resistance persists for a much longer time in untreated, newly infected individuals (many months) than in patients interrupting therapy after treatment failure (many weeks).[5,7] This difference in virus persistence is probably due to the lack of an archived drug-sensitive strain that can rapidly re-emerge in newly infected individuals. Thus, drug-resistance assays should be routinely used when the patient presents within the first year after infection. Even though many newly diagnosed individuals do not know the timing of their infection and had no clear symptoms of primary HIV infection, the use of resistance tests is still justified to determine the presence of drug resistance and to avoid the selection of inappropriate and/or ineffective treatment regimens.

Additional benefits are apparent for the use of resistance testing in antiretroviral-naïve individuals, even beyond the first year after infection. In addition to detecting drug-resistance transmission, resistance assays also provide important information on other virus characteristics that affect patient management. Phenotypic drug resistance assays can also demonstrate subtle reductions in drug susceptibility to non-nucleoside reverse transcriptase inhibitors (NNRTIs) and some protease inhibitor (PI) drugs in wild-type viruses without defined resistance mutations.[3,5] The clinical relevance of the slightly reduced susceptibility among wild-type viruses has not yet been defined, but such reductions are common (occurring in up to 25 percent of wild-type viruses) and they do overlap with clinically relevant ranges of reduced susceptibility observed among drug-resistant viruses after treatment failure. Some phenotypic assays, such as the PhenoSense HIV, also provide information on the replication capacity (a measure of viral "fitness") of the individual's virus, which may have some prognostic value and a role in patient-management decisions.[7,8]

Genotypic assays can detect mutations or polymorphisms that are associated with prior drug resistance and higher risk for emergence of drug resistance during therapy. For example, numerous studies of patients after discontinuation of failing NRTI therapy have demonstrated that a common reverse transcriptase mutation, T215Y, often partially reverts to another mutation, such as T215D, T215S, or T215C, rather than reverting completely to T215.[3,9] Although these "partial revertant" mutations do not cause drug resistance, their detection is very suggestive of prior NRTI resistance, even in the absence of prior therapy. Thus, these mutations may indicate an archived population of drug-resistant virus in the patient and a greater risk of rapid drug resistance emergence after initiation of NRTI therapy.

Even when no drug resistance is defined prior to initiating treatment, establishing a baseline susceptibility profile can be extremely important for future evaluation of the etiology of treatment failure in the patient. The lack of baseline resistance data will preclude the future determination of whether first treatment failure is associated with the emergence of new drug resistance (i.e., a change in drug susceptibility from pre-treatment baseline) or is due to other factors (i.e., no change in drug susceptibility profile).

Finally, the choice of resistance assays for use in management of ARV-naïve patients is complex due to the factors described above. Ideally, both genotypic and phenotypic assays would be used to get a complete assessment of the quantitative drug susceptibility profile (phenotype) as well as the presence of genetic polymorphisms that may predict more rapid treatment failure (genotype). Regardless of the assay used, the clinician should be aware of the limitations of either assay and the importance of obtaining resistance data as close to the date of initial infection as possible. If only one assay is used, the clinician should strongly consider obtaining results from the other assay if the clinical setting is complex (as in the case of known exposure to an individual with extensive treatment history or known drug-resistant virus infection) or if the results of the first assay are unclear (as in the case of the presence of numerous genotypic mutations or minor reductions in phenotypic susceptibility).

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(continued on page 98)

The HIV-Testosterone Link

RICHARD S FERRI, PHD, ANP, ACRN, FAAN

It is well known that the longer HIV disease advances, the more the level of the hormone testosterone declines. In the age of highly active antiretroviral therapy (HAART), when so many patients are living better and longer, HIV treatment has evolved to include long-term symptom management to both improve a person's quality of life and to support treatment adherence.

A deficiency in testosterone levels can lead to a decreased sex drive, erectile dysfunction, depression, loss of muscle mass, and fatigue. These issues are of great concern to most people living with HIV disease because they can hinder the development or continuation of intimate relationships with others.

The cause of testosterone deficiency in HIV disease is thought to be multifactorial. Systemic disease, malnutrition, and wasting are common in HIV disease and are causes of central gonadotropin suppression.

The ADAM (Androgen Deficiency in Aging Men) questionnaire, a preliminary testosterone-screening tool, has been developed by researchers at St. Louis University to assess testosterone levels in men and to determine whether further screening is warranted. (The questionnaire is shown in the sidebar.) A "yes" answer to questions 1 and 7 plus a "yes" response to three or more other questions indicate a need for further screening. Many clinicians advocate routine testosterone screening in HIV-infected individuals since it is such a common clinical problem.

To determine the correct testosterone level in men it is important to understand that there are three forms of testosterone circulating in the blood:

- Sixty percent of testosterone in men is bound tightly to a protein called sex hormone–binding globulin (SHBG).
- About 38 percent is weakly bound to another protein called albumin.
- About 2 percent circulates freely in the bloodstream.

Measurement of total testosterone levels will provide a clearer clinical picture. Testing should be done to determine levels in all three areas because finding an abnormal testosterone level in only one of the three areas may not yield the correct diagnosis.

> A deficiency in testosterone levels can lead to a decreased sex drive, erectile dysfunction, depression, loss of muscle mass, and fatigue.

Replacement therapy for androgen deficiency can be accomplished in several ways. The first and least expensive is by intramuscular injection of testosterone cypionate or enanthate starting at a dose of 200 mg to 300 mg every 2 to 3 weeks. However, the injection may be painful due to the viscous nature of the product. Another drawback is that when injectable testosterone is used, there tends to be a spike in hormone levels for a couple of days following the injection, and then levels drop as the hormone is absorbed.

Another method of replacing testosterone involves the use of a transdermal patch that is changed daily; the patch delivers a more consistent level of testosterone than is provided by intramuscular injection. It should be applied to clean and intact skin with daily site rotation to prevent any skin irritation from developing. The patch should not be placed over any bony prominence because blister formation has been reported.

There is also a gel form of testosterone. The gel is applied daily to clean, dry, and intact skin. This form of treatment also delivers a steady state of the hormone and does not produce any "peaks." Men should be taught to wash their hands carefully after gel application to avoid transmitting the testosterone to pregnant females.

It should be carefully noted that testosterone replacement, regardless of treatment method, is contraindicated in patients with breast carcinoma, prostate cancer, and suspected prostate cancer, as well as in patients with heart, liver, or kidney disease.

See Dr Ferri's bio on page 94. N

Editor's Note: Please see the related article in the nutrition section and the table of anabolic treatments, elsewhere in this issue.

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The following materials were used in the preparation of this article:

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Screening Questionnaire

- Do you have a decrease in libido (sex drive)?
- Do you have a lack of energy?
- Do you have a decrease in strength and/or endurance?
- Have you lost height?
- Have you noticed a decreased "enjoyment of life"?
- Are you sad and/or grumpy?
- Are your erections less strong?
- Have you noticed a recent deterioration in your ability to play sports?
- Are you falling asleep after dinner?
- Has there been a recent deterioration in your work performance?

BRAND NAME	GENERIC NAME	USE	DOSE	CONTACT INFORMATION
Androderm®	Testosterone transdermal system	Androgen deficiency	2.5 to 5.0 mg delivered by patch every 24 hours	Watson Pharmaceuticals (800) 454-2436 www.androderm.com
Androgel®	Testosterone gel	Androgen deficiency	2.5 to 5.0 gm packets every 24 hours	Unimed (770) 578-9000 www.androgel.com

The information contained herein is not intended to be a substitute for professional medical advice. You should not use this information to diagnose or treat a health problem or disease without consulting with a qualified healthcare provider. Please consult your healthcare provider with any questions or concerns you may have regarding your condition.

Risky Cocktails

GUY PUJOL and BILL VALENTI, MD

The use of recreational or "street" drugs is growing to epidemic proportions in many sectors of society. Many people who use these drugs as a means to "party" do so without understanding the impact on their immune health and their HIV drug regimen. Many street drugs can dramatically alter the concentrations of anti-HIV agents, can cause significant damage, and can increase side effects. Clinicians need to educate patients about these interactions and spread awareness in their communities. The "Risky Cocktail" chart below provides a comprehensive overview of interactions and their consequences.

RECREATIONAL / STREET DRUG / ABUSED PRESCRIPTION	PRESCRIPTION MEDICATION	INTERACTION	COMMENTS	REFERENCES
Alcohol	ABC / Ziagen™ / abacavir	Increases ABC levels in blood. One study observed a 41% increase in ABC [1].	ABC is metabolized by alcohol dehydrogenase, thus increasing ABC levels.	[1] McDowell JA, Chittick GE, Pilati-Stevens C, Edwards KD, Stein DS. Pharmacokinetic interaction of abacavir (1592U89) and ethanol in human immunodeficiency virus-infected adults. Antimicrob Agents Chemother 2000; 44:1686-1690.
Alcohol	Protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Acute ingestion of alcohol leads to enzyme (CYP2E1 and 3A4) inhibition.	Chronic ingestion leads to enzyme induction, which may result in sub-therapeutic levels of PIs and NNRTIs.	
Amphetamines	Protease inhibitors (PIs)	2x to 3x amphetamine build-up in blood.	Inhibits CYP2D6 metabolism [2]. Increased likelihood of overdose: hypertension, hyperthermia, seizures, arrhythmia, tachycardia, and tachypnea may be seen as a result.	[2] Lin LY, Di Stefano EW, Schmitz DA, Hsu L, Ellis SW, Lennard MS, et. al. Oxidation of methamphetamine and methylene dioxymethamphetamine by CYP2D6. Drug Metab Dispos 1997; 25:1059-1064.
Amphetamines and cocaine	Selective serotonin reuptake inhibitor (SSRI) antidepressants (e.g., Zoloft®, Paxil®, Prozac®)	Combination may increase serotonin release, resulting in serotonin syndrome [3].	Both metabolized through CYP2D6.	[3] Nolan S, Scoggin JA. Serotonin syndrome: recognition and management. US Pharmacist 1998; 23:2.
Anabolic steroids	RTV / Norvir® / ritonavir	2x to 3x increase of anabolic Sreoids in blood.		See FDA label at: www.norvir.com
Antidepressants (tricyclic)	RTV / Norvir / ritonavir	Inhibits metabolism of antidepressants; increases plasma antidepressants' concentrations.		See FDA label at: www.norvir.com
Barbiturates	Protease inhibitors (PIs)	Increases blood levels of barbiturates.		
Ecstasy / X / E / MDMA	MAOI Antidepressants (Nardil®, Marplan®, or Parnate®)	Increases levels of both MAOIs and MDMA.	Decreases CYP2D6 metabolism.	
Ecstasy / X / E / MDMA	RTV / Norvir / ritonavir	3x to 10x increase of MDMA in blood.	Interferes with (decreases) CYP2D6 metabolism. Toxicities include hyponatremia, hyperthermia, arrhythmia, tremor, hyperreflexia, sweating, seizures, and tachycardia. At least one reported death from MDMA/RTV interaction [4].	[4] Henry JA, Hill IR. Fatal interaction between ritonavir and MDMA. Lancet 1988; 352:1751-1752.
Gamma hydroxybutyrate / GHB / Liquid X ("Date rape drug")	Protease inhibitors (PIs)	5x to 10x increase of GHB.	One case of GHB toxicity with RTV/SQV [5]. Overdose symptoms include myoclonic or seizure activity, bradycardia, respiratory depression, or loss of consciousness.	[5] Harrington RD, Woodward JA, Hooton TM, Horn JR. Life-threatening interactions between HIV-1 protease inhibitors and the illicit drugs MDMA and gamma-hydroxybutyrate. Arch Intern Med 1999; 159:2221-2224.
Heroin	RTV / Norvir / ritonavir	Decreases heroin levels by 50%.	Heroin rapidly converts to morphine by plasma and liver esterases. Expect interactions once converted to morphine. Watch for opiate withdrawal.	See web site of HarmReduction.org at: www.harmreduction.org/issues/health/haartmeth/haartmethmain.html
Ketamine / K / Special K	Protease inhibitors (PIs)	Build-up of K in blood with antiretrovirals, especially RTV, NFV, and EFV.	CYP2B6 is main metabolic enzyme. 3A and 2C9 are utilized to a lesser extent [6].	[6] White PF, Way WL, Trevor AJ. Ketamine: its pharmacology and therapeutic uses. Anesthesiology 1982; 56:119-136.
Ketamine / K / Special K	RTV / Norvir / ritonavir	Build-up of Ketamine likely.	Overdose symptoms include respiratory depression, loss of consciousness, and hallucinations.	
Lysergic acid diethylmide / LSD	Protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs)	PI and NNRTI CYP450 inhibitors may cause build-up of LSD.	Overdose symptoms include hallucinations, agitation, psychosis, and "flashbacks."	
Marijuana	Protease inhibitors (PIs)	Increases THC (active compound in marijuana) levels.	Decreased metabolism of THC by PIs; therefore, smaller amounts of THC required for medicinal purposes.	
Marijuana	Protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Smoked marijuana may lower PI and NNRTI levels. Smoked THC in one study decreased NFV by 17% and IDV by 21% [7].	THC interferes with CYP3A4, 2C9, and 2D6. Increases in THC if using medications that inhibit CYP450; decreases in THC if using medications that induce CYP450.	[7] Kosel BW, Aweeka FT, Benowitz, Shade SB, Hilton JF, Lizak PS, et. al. The effects of cannabinoids on the pharmacokinetics of indinavir and nelfinavir. AIDS 2002; 16:543-550.
Phencyclidine / PCP	Protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Possible increased levels of PCP in blood.	Overdose symptoms include seizures, hypertension, rhabdonyolysis, and hyperthermia. Metabolism by CYP3A and CYP2C11; inhibits CYP2B1 [8].	[8] Laurenzana EM, Owens SM. Metabolism of phencyclidine by human liver microsomes. Drug Metab Dispos 1997; 25:557-563.
Poppers / amyl nitrate	Viagra®	Decreases blood pressure. Can be fatal.	Nitrate compounds should not be used with Viagra.	See: www.viagra.com (go to Patient Product Information).
Rohypnol ("Date rape drug")	RTV / Norvir / ritonavir	2x to 3x increase of Rohypnol in blood.		
Sedatives	Protease inhibitors (PIs)	Inhibits metabolism of sedatives; increases plasma concentrations.		
Speed / crystal meth / Tina	RTV / Norvir / ritonavir	2x to 3x increase of crystal meth in blood.		
Temazepam / jellies	RTV / Norvir / ritonavir	Temazepam metabolized more quickly.		
Valium® / diazepam	RTV / Norvir / ritonavir	Increase in blood levels of diazepam.		
Viagra®	Protease inhibitors (PIs), in particular RTV / Norvir / ritonavir	4x increase of Viagra in blood.	Start with Viagra 25 mg instead of usual 50 mg dose in conjunction with protease inhibitors.	See: www.viagra.com (go to Patient Product Information).

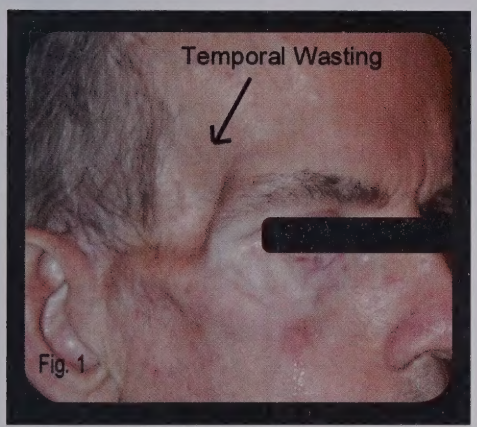
(continued on page 99)

Treatment Options in HIV-Related Facial Lipodystrophy

OLEH SLUPCHYNSKYJ, MD

Highly active retroviral therapy (HAART) with protease inhibitors, introduced in 1996, dropped mortality rates by 45 percent within the first year of their use.[1,2] Unfortunately, HAART treatment has been associated with a disfiguring side effect known as HARS (HIV-related fat-redistribution syndrome).[3]

Clinically, HARS is characterized by a progressive loss of subcutaneous fat involving the face, extremities, and buttocks and an excess of fat



deposition in the abdomen, breasts, and neck. As many as 64 percent of patients infected with HIV who are treated with HAART will experience some form of HARS. By far, the most stigmatizing characteristic of HARS is associated with fat loss and redistribution in the face. Facial lipodystrophy is associated with other rare diseases and was described as early as 1963. However, facial lipodystrophy has become more prevalent, due to HIV treatment, and is typically associated with HIV infection. Patients with facial lipodystrophy have reported psychological disturbances including depression, anxiety, social isolation, reduced confidence and self worth, and lack of sexual interest, all of which can secondarily suppress immune function.

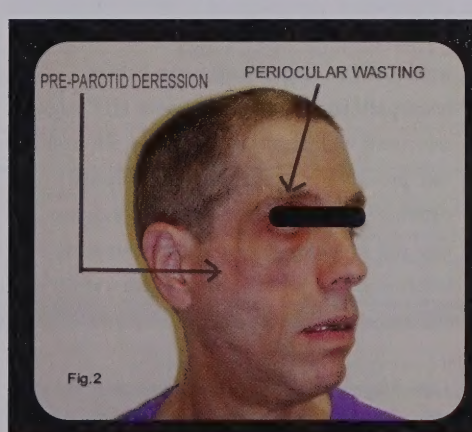
Facial lipodystrophy can be divided into two categories: facial wasting and facial fat deposition. Facial wasting includes subcutaneous fat loss in the areas of the temple (Fig. 1), preparotid, periorbita (Fig. 2), and submalar (Fig. 3). Facial fat deposition includes fat accumulation in the submental area (Fig. 4), post-auricular area, and dorsocervical area.

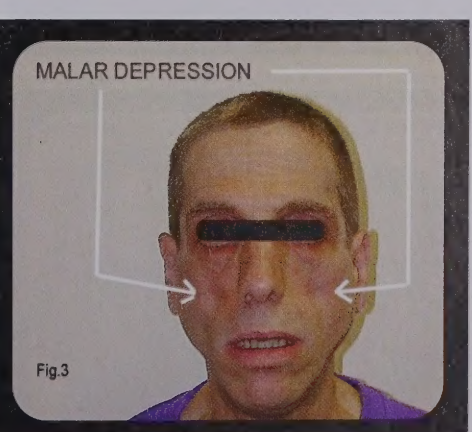
Treatments for facial lipodystrophy include facial liposuction or facial augmentation.

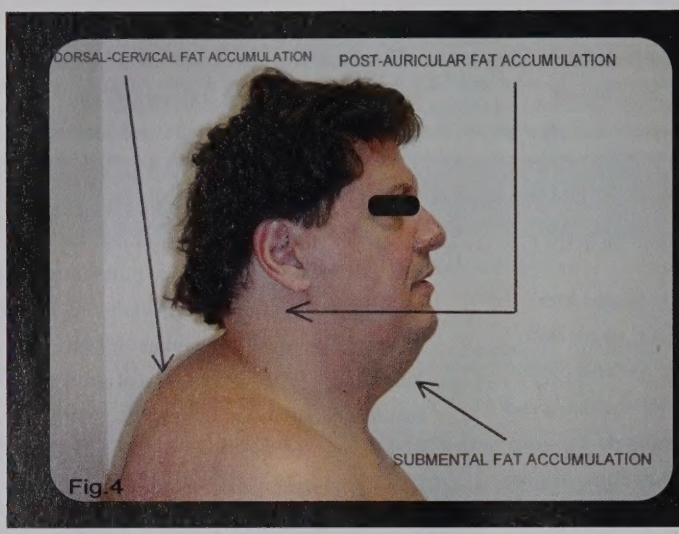
Facial fat deposition is easily treated with simple liposuction of the neck, upper back, and postauricular areas (Fig. 5). This procedure is performed under local anesthesia and mild sedation. After the procedure, patients can go home with an escort and they require minimal wound care. Immediate recovery time is about 12 hours to allow any intravenous medications to wear off. There is mild bruising for about 5 to 7 days. Swelling decreases about 50 percent in the first week, 90 percent in the first month, and 100 percent in the first 3 months. Other potential, but rare, complications can include brief weakness of the lip, hematoma (blood collection under the skin), and infection. There is also little or no pain involved in this procedure. Cost for this procedure can range from $2500 to $4000.

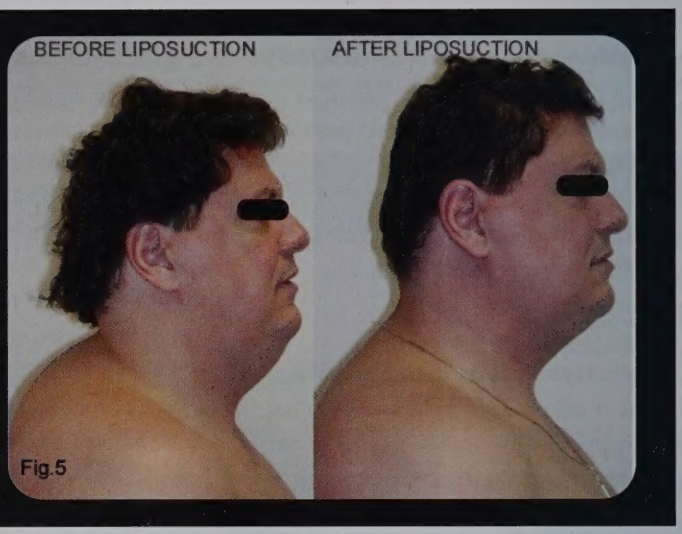
Facial wasting is primarily treated with fillers or facial implants. Fillers include collagen, fat injections, Restylane®, Perlane®, Artecoll®, Alloderm®, Cymetra®, silicone, and a substance presently being used in Europe and Mexico called New-Fill®. All of these fillers are injected and can vary with regard to longevity, pain associated with injection, and potential side effects. The most common substances used for facial wasting include collagen, silicone, and New-Fill. Silicone and New-Fill injections are not presently approved by the FDA in the US. New-Fill has shown promising results in European trials. It is made of polylactic acid (PLA), the same substance used to make suture material. It is immunologically inactive, biocompatible, and absorbable. New-Fill (PLA) is injected into areas of wasting in 4 treatment sessions spaced 4 weeks apart. PLA is absorbed and destroyed by the body and leaves a collagen matrix or scar tissue in the area of injection. Therefore, the filling material left behind is one's own tissue. New-Fill is showing promising results as far as longevity; however, well designed statistical data has yet to be published. Collagen, derived from cows, is a good alternative, although it only last 3 to 4 months and can be quite costly. Silicone is also used by some practitioners, but it can have life-long sequelae if not injected properly. Other injectables mentioned are less commonly used and are not permanent aside from Artecol®. Costs for injectable fillers can range from $500 a treatment to more than $2500.

Facial implants have been used safely and effectively in cosmetic surgery for over 20 years. Implants are generally made of an inert material such as silastic or Gore-Tex. Gore-Tex implants are used not only in facial implants but also in vascular and general surgery. They are porous and there is some ingrowth of

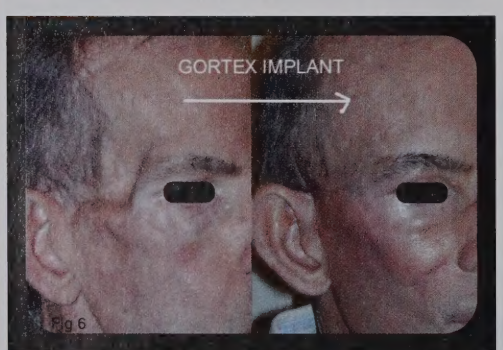








tissue, which makes the implant less likely to move once in position and easy to remove if this is needed. Silastic implants can also be used safely, but are more likely to move around if not placed properly. Facial implantation is performed with light sedation and local anesthesia. Associated complications include infection and temporary loss of sensation over the cheek area. Gore-Tex augmentation of the temple and cheek areas is shown in Figures 6 and 7. There is complete correction of the cheek and temple depression with 100 percent patient satisfaction. Although there is correction of the temple and cheek, the preparotid and periocular areas are not corrected. These areas may be further corrected with fillers such as collagen or New-Fill.



One other implant/filler that deserves mentioning is alloderm. Alloderm is derived from cadaveric skin and comes in 4 x 4 cm or 4 x 6 cm sheets. However, alloderm is not permanent, and the amount needed for such augmentation would make it cost prohibitive. The price range for facial implants can range from $3500 to more than $6500, depending on how many areas are augmented.

Facial lipodystrophy can have a devastating psychological impact on HIV patients and in turn can depress an already stressed immune system. Facial augmentation can help to restore self confidence and remove HIV stigma associated with facial lipodystrophy. All healthcare providers working with HIV-infected patients should be aware of facial lipodystrophy and should provide their patients with information about treatment of this socially and emotionally debilitating disorder.

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Treatment for Metabolic/Wasting Disorders in HIV

BILL VALENTI, MD

This table provides a list of drugs that are commonly used to treat metabolic and wasting disorders in HIV/AIDS. Not all of these drugs have a labeled indication for HIV/AIDS wasting disorders from the US Food and Drug Administration. Labeled indications are noted at the end of each drug's listing. (Drug classes and drugs are listed alphabetically.)

ANABOLIC STEROIDS (ORAL)	STANDARD DOSING	SPECIAL CONSIDERATIONS
Anadrol®-50		
oxymetholone Unimed Pharmaceuticals www.anadrol.com	1–5 mg/kg per day	Metabolized by the liver: liver function tests should be monitored during therapy. Contraindicated in pregnancy.
US FDA labeled indication: Treatment of anemias caused by deficient red cell production.		
Oxandrin®		
oxandralone BTG Pharmaceuticals www.oxandrin.com/	2.5 mg 2–4 times a day	Testosterone analog with potent anabolic and minimal androgenic side effects. Dose can be increased depending on patient need. Metabolized by the liver: liver function tests should be monitored during therapy. Liver function abnormalities minimized with doses less than 20 mg/day.
US FDA labeled indication: Adjunctive therapy to promote weight gain after weight loss following extensive surgery, chronic infections, or severe trauma		
Winstrol®		
stanozolol Sanofi Syntelabo www.sanofi-synthelabous.com/	2 mg 3 times a day	Metabolized by the liver: liver function tests should be monitored during therapy.
US FDA labeled indication: Prophylactically to decrease the frequency and severity of attacks of angioedema.		
ANABOLIC STEROIDS (GEL)	**STANDARD DOSING**	**SPECIAL CONSIDERATIONS**
AndroGel®		
1% dihydrotestosterone gel Unimed Pharmaceuticals www.androgel.com	One 5-gram packet (50 mg testosterone) daily	Can adjust the dose based on testosterone levels after treatment. Applied to arms, shoulders or abdomen. Option for testosterone replacement to avoid injections.
US FDA labeled indication: Replacement therapy in males with deficiency or absence of endogenous testosterone.		
ANABOLIC STEROIDS (INJECTABLE)	**STANDARD DOSING**	**SPECIAL CONSIDERATIONS**
Deca Durabolin		
nandralone decanoate Watson Pharma www.watsonpharm.com	Men: 50–200 mg at 1–4 week intervals Women: 50–100 mg at 1–4 week intervals	Potent androgen with virilizing side effects in women. Resistance exercises with Deca Durabolin will help maximize weight gain as lean muscle.
US FDA labeled indication: Anemia due to renal insufficiency.		
Depo®-Testosterone		
testosterone cypionate Pharmacia www. pnu.com	50–400 mg every 2–4 weeks	Potent androgen with virilizing side effects in women. Resistance exercises with Depo-Testosterone will help maximize weight gain as lean muscle. Suggested starting dose: 100 mg every 1–2 weeks. Some patients may experience so-called "testosterone surge" or "rush" within an hour of injection.
US FDA labeled indication: Replacement therapy in males with a deficiency or absence of endogenous testosterone.		
ANABOLIC STEROIDS (PATCH)	**STANDARD DOSING**	**SPECIAL CONSIDERATIONS**
Androderm®		
testosterone transdermal system Watson Pharma www.androderm.com	One 5 mg patch/day	Can be applied to back, abdomen, arms or thighs. Occasional skin irritation reported. Option for testosterone replacement to avoid injections.
US FDA labeled indication: Replacement therapy in males with a deficiency or absence of endogenous testosterone.		
Testoderm TTS®		
testosterone transdermal system (TTS) ALZA Pharmaceuticals www.alza.com	One 5 mg patch/day	TTS system has replaced scrotal patch. Can be applied to arm, back, or upper buttocks. Occasional skin irritation reported. Option for testosterone replacement to avoid injections.
US FDA labeled indication: Replacement therapy in men with a deficiency or absence of testosterone.		
Notes: Drugs in the above groups are all synthetic derivatives of testosterone. All drugs in the above groups may increase blood lipids. Fasting lipid profile should be done prior to initiating these drugs and during treatment.		
APPETITE STIMULANTS (ORAL)	**STANDARD DOSING**	**SPECIAL CONSIDERATIONS**
MARINOL®		
dronabinol Unimed Laboratories www.marinol.com	2.5 mg twice a day before afternoon and evening meals	Potent appetite stimulant. Often used in combination with anabolic agents. Can add to effects of other CNS depressants such as alcohol and sedatives resulting in increased sedation. Maximum dose up to 20 mg/day in divided doses.
US FDA labeled indication: Anorexia associated with weight loss in patients with AIDS; nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond to conventional antiemetic treatments.		
MEGACE®		
megestrol acetate oral suspension Bristol-Myers Squibb www.bms.com/products/data/	800 mg a day	Once a day oral formulation. Synthetic progesterone derivative. Contraindicated in pregnancy and for nursing mothers. Male hypogonadism: males should have free and total testosterone checked before starting this drug.
US FDA labeled indication: Treatment of anorexia, cachexia, or unexplained, significant weight loss in patients with AIDS.		
GROWTH HORMONE (INJECTABLE)	**STANDARD DOSING**	**SPECIAL CONSIDERATIONS**
SEROSTIM®		
recombinant human growth hormone (r-hGH) injection Serono Laboratories www.seronousa.com	5–6 mg IM per day	Usually given in 12 week cycles, but can be used for longer periods. Resistance exercise will maximize benefits of growth hormone. Bioelectrical impedence analysis (BIA) should be done prior to starting treatment and followed during treatment. Side effects are minimal with 3–6 months of therapy, but fluid retention and edema, carpal tunnel syndrome, and muscle aching have been reported.
US FDA labeled indication: AIDS wasting or cachexia. Off label note: Lower doses (i.e., 2–3 mg/day) have been used for wasting and for lipodystrophy.		

Cervical Cancer in HIV-Positive Women

LYN STEVENS, MS, ACRN, NP

Cervical cancer may be the most common AIDS-related malignancy in women. Although not an uncommon diagnosis in women in the general population, the New York City AIDS Surveillance data from 1990–1995 found that the observed cervical cancer cases in HIV-positive women were two to three times higher than the expected number of cases.[1] Findings such as these resulted in the inclusion of cervical cancer in the Centers for Disease Control and Prevention (CDC) expanded definition of AIDS in 1993.[2]

Women with HIV and cervical cancer tend to be younger than their HIV-negative counterparts. When compared with HIV-negative women, HIV-positive women with invasive cervical cancer appear to present at more advanced stages (especially with a CD4 <200/mm^3), metastasize to unusual locations, such as the psoas muscle, or clitoris, have poorer responses to standard therapy, and have higher recurrences and death rates, as well as shorter intervals to recurrence or death.[2,3]

Women in general have the following risk factors for cervical cancer: cigarette smoking, having multiple sex partners, having partners who have had multiple sex partners, and immunodeficiency conditions such as those associated with HIV/AIDS. Although studies have come to varied conclusions concerning the risk factors that are associated with increased incidence of cervical dysplasia or cervical cancer in HIV-infected women, a study conducted by Davis et al. using a multivariate statistical analysis ruled out high viral loads as a significant risk factor. CD4 cell counts were found to be the only independent prognostic factor for development of cervical dysplasia or carcinoma.[4] Viral load does not seem to have an impact on incidence; however, decreased CD4s are associated with higher risk. Our most current information suggests that the most significant risk factor for cervical cancer is infection with human papilloma virus (HPV).

HPV is a common infection in the general population. Current evidence suggests that over 50 percent of sexually active adults have been infected with one or more HPV types. In HIV-positive women, the prevalence and persistence of HPV infection increase with decreasing CD4 count and increasing HIV RNA levels. According to a population-based prospective study published recently, HPV precedes development of cervical cancer.[5]

Cervical cancer often presents with no obvious signs. When symptoms do occur, they may include abnormal vaginal bleeding or discharge, or pain or bleeding after sexual intercourse. However, cervical cancer can often be prevented or detected in its earliest stages through effective screening with a Pap smear and avoidance of known risk factors.

Certainly this accentuates the importance of routine GYN care for HIV-infected women.

The Centers for Disease Control and Prevention (CDC) recommend complete GYN evaluation, including a Pap smear, as part of the initial HIV evaluation or upon entry to prenatal care.[6] The Pap smear should be repeated 6 months later. If both smears are negative, annual screening is recommended thereafter in an asymptomatic woman. More frequent screening—every 4 to 6 months—is recommended for women with prior abnormal Pap smears, with signs of HPV infection, after treatment for cervical dysplasia, with symptomatic HIV infections, and with CD4 counts <200/mm^3.

In healthcare settings that treat those diagnosed with HIV infection, 30–60 percent of Pap smears exhibit cytologic abnormalities and 15–40 percent have evidence of dysplasia; these rates are 10 to 11 times greater than those observed among HIV-negative women.[7] Pap smears that show atypia, dysplasia, atypical squamous cells of uncertain significance (ASCUS), squamous intraepithelial lesion (SIL), or cervical intraepithelial neoplasia (CIN) should be investigated by a trained colposcopist. For a complete GYN evaluation, screening for sexually transmitted diseases should be added. Cultures for gonorrhea and chlamydia, "wet mount" for trichomoniasis, and serology for syphilis should be included.

Recommendations for cervical cancer screening for HIV-infected women also suggest that HPV testing be done along with the first two Pap smears within the first year after HIV diagnosis. Based on the test results, future screenings should be added at routine intervals. The OI or STD guidelines do not offer specifics for HPV follow-up. This concept is clinically efficacious and cost-effective.[8]

Treatment for all women with cervical cancer includes surgery and/or combined radiation therapy and chemotherapy. An additional consideration for HIV-positive women is Highly Active Antiretroviral Therapy (HAART). To date, researchers report conflicting results as to whether placing a woman on therapy will delay or prevent cervical cancer. In 1998, Heard and colleagues completed a study that demonstrated a statistically significant decrease in cervical precursor lesions and in colposcopic abnormalities in 49 HIV-infected women after use of HAART for a median of 5 months. Precursor lesions were more likely to regress in those women who experienced increase in CD4 cell count after initiating HAART.[9] Another study conducted by Heard and colleagues published in 2002 to investigate the impact of HAART on the regression of cervical intraepithelial neoplasia (CIN) in HIV-infected women again demonstrated the positive impact of HAART on CIN regression, probably associated with some restoration of specific immune reactivity.[10] However, the International Collaborative Study analyzed data from 11 international cohort studies on AIDS-related malignancies and found no decrease in cervical cancer coincident with the widespread availability of HAART.[11] It is possible, however, that reversing HIV-associated immunosuppression might reduce HPV persistence and consequently decrease the risk for cervical neoplasia among HIV-seropositive women.[12]

Frequently, the challenge in providing routine GYN care is getting the patient into the office for the initial workup and then providing follow-up care. The New York State Department of Health AIDS Institute has published a booklet, "Promoting GYN Care for HIV-Infected Women: Best Practices from New York State."[13] This booklet is designed to supply healthcare practitioners who provide or design healthcare services for women with HIV/AIDS with practical solutions to the problems of attracting and retaining women in GYN care. This booklet is available online at: www.hivguidelines.org.

It is clear that cervical cancer in HIV-infected women can often be prevented or detected in its earliest stages through effective screening with a Pap smear, routine testing for HPV, and avoidance of known risk factors. It is our charge, then, to implement such screening as appropriate.

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Discontinuing Prophylaxis for Opportunistic Infections in the HAART Era

AMNERIS E LUQUE, MD

The prevention of opportunistic infections (OIs) was one of the first success stories in AIDS care. Early in the AIDS epidemic, *Pneumocystis carinii* pneumonia (PCP) occurred in 75 percent of patients with the syndrome[1] and was fatal in many cases. Clinical studies in the late 1980s outlined the risk factors associated with the development of PCP and allowed clinicians to concentrate their efforts on identifying these risk factors and instituting prophylaxis for people at risk.[2] As a result of the widespread use of prophylaxis, the number of new cases of PCP declined after 1988, preventing or delaying death from this infection. Central nervous system infections with *Toxoplasma gondii* were also successfully prevented by first-line regimens used to prevent PCP.

Although death from PCP was prevented, the immune system continued to deteriorate in the absence of effective antiretroviral therapy, and infections with agents that developed with profound immunosuppression were frequently encountered. Disseminated infection with *Mycobacterium avium* complex (MAC) was recognized as the most common bacterial opportunistic infection in patients with advanced stages of AIDS. Several clinical studies in the second decade of the epidemic outlined successful regimens for prevention of MAC infections.[3–5]

Prophylaxis treatments for systemic fungal infections with *Cryptococcus neoformans* are routinely used only in regions of high prevalence due to concerns of cost-effectiveness and the risk of developing resistance. Prophylaxis for infections with Cytomegalovirus (CMV) did not become widespread before HAART became available. A substantial decline in the incidence of CMV quickly followed the advent of HAART, and thus large trials on prevention have been slow to recruit subjects.

With the use of HAART, the incidence of new cases of PCP, disseminated MAC, and CMV infections was drastically reduced, whereas rates of use of prophylaxis for PCP, MAC, and CMV remained constant, confirming the effectiveness of potent antiretroviral therapy on this unprecedented decline in morbidity.

Before the success of combination antiretroviral therapy was documented, prophylaxis for opportunistic pathogens continued indefinitely. However, the use of HAART reduces the levels of HIV RNA in plasma (HIV viral load) and increases CD4 counts within weeks of initiating treatment. Whether all CD4 cells that recovered after initiation of HAART were functional was debated for some time. Arguments calling for caution speculated that the initial CD4 cell increase could be limited to CD4 cell populations that were not involved in the prevention of OIs. Other groups published reports of complete normalization of CD4 counts several months after effective HAART.[6,7]

Our new understanding of CD4 cell recovery prompted questions about the feasibility of discontinuing prophylaxis for OIs. Several observational cohort studies addressing this question have suggested that it is safe to discontinue prophylaxis against PCP in those patients who have sustained an increase in CD4 counts in response to HAART.[8–10] A subsequent randomized trial on the discontinuation of primary and secondary prophylaxis against PCP recently confirmed the results of the previous observational cohorts, demonstrating a low risk of developing recurrent PCP among patients who have sustained increases in CD4 cell counts to greater than 200 x 106/l.[11]

Similarly, two randomized, controlled studies on the discontinuation of MAC prophylaxis have suggested that it is safe to discontinue primary prophylaxis against MAC in those patients who have had a CD4 T cell increase to >100 cells/cu mm for at least 3–6 months on HAART.[12,13] Although these studies have not found a significant increase in the incidence of MAC disease during a median of 12–16 months of follow-up, atypical manifestations of MAC were reported in a few patients after discontinuation of both primary and secondary prophylaxis requiring retreatment for MAC.

It is now accepted that the increase in CD4 cell counts after HAART is probably due to redistribution of memory cells followed by an increase in diversity of the T cell repertoire. Production of naïve cells and complete immune restoration occurs over the 6 months following initiation of HAART.[7] This understanding of the CD4 cell kinetics in response to HAART, together with the results of the clinical studies outlined above, are the basis for the current guidelines regarding discontinuation of prophylaxis for OIs.[14]

A few reports of successful discontinuation of maintenance therapy for disseminated MAC infection and toxoplasma encephalitis in patients responding to HAART have been published; these reports, although encouraging, included a limited number of patients and did not allow for generalization.[15,16] A recent retrospective study conducted in several HIV clinics in Canada found a very low rate of recurrence of disseminated MAC infections in 52 patients with a favorable response to HAART in whom treatment for MAC had been stopped.[17] In this retrospective review, only one patient developed recurrent MAC infection 37 months after discontinuing MAC treatment and 2 months after discontinuing HAART.

A large observational study conducted in Europe also showed low recurrence rates for CMV end-organ disease, disseminated MAC infection,

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TABLE 1. Recommendations for Discontinuation of Prophylaxis of Opportunistic Infections

Opportunistic Infection	Discontinuation of Primary Prophylaxis	Discontinuation of Secondary Prophylaxis
PCP	Patient receiving HAART with increase in CD4 count to greater than 200 cells/cu mm for more than 3 months	•CD4 count increase on HAART to greater than 200 cells/cu mm or greater than 14% of total lymphocytes for more than 3 months •Adequate viral suppression •If PCP occurred with CD4 of more than 200 cells/cu mm, prophylaxis should be maintained
Toxoplasma encephalitis (TE)	Patient receiving HAART with increase in CD4 count to greater than 200 cells/cu mm for more than 3 months in response to HAART	•CD4 count of greater than 200 cells/cu mm for more than 3 months in response to HAART •Asymptomatic for TE
MAC	CD4 count increase to greater than 100 cells/cu mm for more than 3 months in response to HAART	•CD4 count increase to greater than 100 cells/cu mm for more than 6 months in response to HAART •Completed at least 12 months of treatment for DMAC* •Asymptomatic for MAC
Cryptococcosis	Not applicable	•CD4 count increase to greater than 100 cells/cu mm for more than 6 months •Completed initial therapy •Asymptomatic for cryptococcosis
Cytomegalovirus (CMV)	Not applicable	•CD4 count greater than 100 to 150 cells/cu mm for more than 6 months •No evidence of active disease •Regular ophthalmic examination

**Obtaining blood cultures or bone marrow cultures may be advisable to ascertain disease activity.*

The Importance of Oral Health in HIV Disease

LOUIS G. DePAOLA, DDS, MS

Publication of the first Surgeon General's Report on Oral Health in the year 2000 is a milestone in the history of oral health in America. "The report elaborates on the meaning of oral health and explains why oral health is essential to general health and well-being. In the course of the past 50 years, great progress has been made in understanding the common oral diseases—dental caries (tooth decay) and periodontal (gum) diseases—resulting in marked improvements in the nation's oral health. Most middle-aged and younger Americans expect to retain their natural teeth over their lifetime and do not expect to have any serious oral health problems."[1] The primary message of Surgeon General's report is that "Oral health is essential to the general health and well-being of all Americans *and* can be achieved by all Americans."

However, *not all* Americans are achieving the same degree of oral health. In spite of the safe and effective means of maintaining oral health that have benefited most Americans over the past half century, many still experience needless pain and suffering, complications that devastate overall health and well-being, and financial and social costs that diminish the quality of life and burden American society. What amounts to "a silent epidemic" of oral diseases is affecting America's most vulnerable citizens—poor children, the elderly, and many members of racial and ethnic minority groups.[1,2] This is especially true of patients infected with HIV.

"Over the past five decades, major improvements in oral health have been seen nationally for most Americans. Despite improvements in oral health status, profound disparities remain in some population groups as classified by sex, income, age, and race/ethnicity.[2] For some diseases and conditions such as HIV, the magnitude of the differences in oral health status among population groups is striking.[1,2] Oral diseases and conditions affect people throughout their life span and have a significant, negative impact on the quality of life. Nearly every American has experienced the most common oral disease, dental caries,"[1] but most have easy access to dental care. Locating a reliable source for quality dental care, however, can be problematic for people with HIV.

A number of factors contribute to this phenomenon. Fear of acquiring HIV from positive patients, perceived lack of expertise to manage HIV-related oral disorders, and inadequate compensation all contribute to barriers for oral care. In the HIV population, maintenance of good oral health is important because patients with HIV and AIDS tend to have a much higher incidence of oral, dental, and periodontal disease.[3] The key to the management of the oral manifestations of HIV disease is regular professional care and meticulous oral hygiene. When a comprehensive program of routine oral hygiene and periodic professional care is implemented, pain, loss of function, and other symptoms that can impair quality of life can be reduced or eliminated. A brief review of the principles of oral hygiene that HIV-infected individuals should follow will be reviewed.

Most Americans have gingivitis, and most adults 25 years and older have periodontal disease.[1,4] At every age, a higher proportion of those at the lowest socioeconomic status (SES) level have more advanced periodontal disease, compared to those at higher SES levels.[5,6] As with the general population, most HIV-infected persons have periodontal disease, and the lower the SES, the more advanced the disease. In addition, more severe and aggressive HIV-related periodontal conditions occur. However, it is unclear whether there are periodontal lesions specific to HIV infection or whether these lesions represent exacerbation of periodontal conditions and disease, such as chronic periodontitis, due to severe immunodeficiency or immunosuppression. HIV-related periodontal conditions include:

Line linear gingival erythema (LGE)[7,8]

Linear erythematous band involving the free marginal gingiva without demonstrable attachment loss. The erythema may extend to attached gingival.

- Possible precursor of necrotizing ulcerative periodontal conditions
- Prevalence: 4% to 50%
- Spontaneous hemorrhage
- Minimal plaque deposits
- Associated with *Candida albicans*
- LGE responds poorly to conventional treatment, such as cleaning, scaling and root planning

Necrotizing Ulcerative Gingivitis[7,8]

- Primarily affects the papillary and marginal gingiva
- Gingival erythema and edema, with spontaneous bleeding
- Yellowish-grayish ("pseudomembranous") areas of marginal and/or papillary necrosis of gingiva
- Loss of interdental papillae
- Pain
- Rapid progression and extension possible

Necrotizing Ulcerative Periodontitis[7,8]

- Prominent changes in gingival contour are associated with tissue necrosis and loss of periodontal attachment and bone
  - Interproximal ulceration, necrosis, and cratering
  - Fetor oris ("bad breath") is often present
  - Pain (severe, deep, localized in jaw)
  - Spontaneous bleeding
- Soft tissue necrosis and rapid periodontal destruction

Importance of Oral Hygiene in Management of Periodontal Disease in HIV Patients

Because periodontal diseases are plaque-associated infections, prevention and management of the early signs of these diseases depend on effective plaque control, which can be accomplished using both mechanical and chemotherapeutic approaches.[1,9] Therefore, meticulous oral hygiene is the cornerstone of periodontal therapy.

The principles of oral health should be introduced as soon as possible after the diagnosis of HIV is confirmed. Daily brushing and flossing to remove plaque, the daily use of over-the-counter fluorides to prevent or reduce caries ("decay"), and regular professional care are all important aspects of routine oral hygiene. Asymptomatic HIV-infected patients should be recalled for periodic evaluations as indicated. The Agency for Health Care Policy and Research (AHCPR) currently recommends that HIV-infected patients be recalled at least two times per year for oral examination and evaluation; it further suggests that with the appearance of oral lesions or other complications, more frequent recall may be indicated. Decreased salivary flow as well as certain medications may increase the incidence of dental caries. Professionally prescribed fluoride supplements or topical applications may need to be considered for such patients, and daily antiseptic mouth rinses accepted by the American Dental Association and bearing their Seal of Approval should be used daily. Such a program may also be considered for patients who are unable to maintain optimum oral health through routine preventive care.[10,11]

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Painful Sensory Neuropathy: A Therapeutic Challenge

HOWARD AARON ARONOW, MD | ELYSE J. SINGER, MD

The most frequent and debilitating neurological complication associated with HIV and antiretroviral treatment is Painful Sensory Neuropathy (PSN). It also is referred to as Peripheral Neuropathy and Distal Symmetric Predominantly Sensory Peripheral Neuropathy (DSPN). When purely associated with antiretroviral treatment so that the condition completely resolves once the neurotoxic antiretroviral treatment is discontinued, the condition is called antiretroviral toxic neuropathy (ATN). The majority of cases of PSN in HIV are of a mixed nature in that they are caused by both HIV and exposure to neurotoxic antiretroviral therapies. The current prevalence of DSPN in HIV is reported at 30 percent regardless of stage of illness, although the incidence has been reported at 52 percent in individuals with CD4+ counts <200 cells/mm^3. In our population of AIDS-defined individuals pre-selected for central nervous system diseases, the incidence of DSPN is nearly 70 percent. Because healthcare providers are often undertrained and poorly equipped to deal with the ever-growing number of people with HIV DSPN and may not be expert in the management of chronic pain, we offer this article to provide guidance in the diagnosis and treatment of DSPN.

Diagnosis

The diagnosis of DSPN is fairly straightforward. The patient will first complain of the insidious onset of numbness and paresthesias involving the feet that progressively gets worse over weeks to months and spreads up the legs. The numbness is then accompanied by burning, electrical, jabbing, freezing, lancinating pain. This pain tends to be worse at night and can be so severe as to be triggered by bedclothes moving against the legs. It rarely involves the upper extremities and is predominantly sensory. In the few cases involving the upper extremities, classic dictum is that the shaded stocking deficit has extended up to or above the knees before there is any glove type deficit in the hands. Any significant weakness of the extremities should alert the examiner to an alternative diagnosis.

On examination, there is a mostly symmetrical shaded stocking deficit to primary sensory modalities, including touch (both dull and sharp), temperature, and vibratory sensation to a 128 Hz tuning fork. Deep tendon reflexes are usually preserved at the knees, but are severely diminished or absent at the ankles. Preservation of ankle jerks (Achilles reflexes) or briskness of these reflexes should again alert the examiner to an alternative diagnosis: the pain and sensory loss in such cases is usually due to spinal cord disease, commonly referred to as Vacuolar Myelopathy, the most commonly associated HIV syndrome of spinal cord injury. This syndrome is usually manifested by lower-extremity spasticity, urinary frequency, constipation, and in the male patient, sexual impotence. There may be proximal weakness and, again, deep tendon reflexes in the lower extremities are brisk and may be pathological with associated clonus and bilateral Babinski responses. When there is significant diffuse weakness, along with loss of all reflexes, then the diagnosis is usually that of a Demyelinating Polyneuropathy. When this is acute, it is known Guillain–Barré Syndrome. When it is more slowly progressive and chronic, it is known as Chronic Inflammatory Demyelinating Polyneuropathy (CIDP).

It is crucial that the examiner be able to differentiate amongst these diagnoses because treatment is different for each of these entities and, especially, because Guillain-Barré and CIDP can be life-threatening when these syndromes involve compromise to accessory respiratory muscles. These demyelinating polyneuropathies require confirmation by delayed late responses in nerve conduction velocity testing (delayed or absent H and F reflexes). Spinal fluid analysis by lumbar puncture (LP) may reveal a lymphocytic pleocytosis (elevation of white blood cells) that would be indicative of an inflammatory response. These conditions are treated with high-dose intravenous gamma globulin (IVIG), with or without plasmapheresis, which is meant to quell an autoimmune attack against the myelin coating of peripheral nerves.

Vacuolar myelopathy may require confirmation by performing Magnetic Resonance Imaging (MRI) scans of, at minimum, the thoraco-lumbar spinal cord to see the termination of the spinal cord; MRI scans of the cervical cord may also be required, especially if there is any question of upper-extremity involvement. These scans should be normal or at least show no evidence of mass lesion, hemorrhage, or infection. In addition, LP may reveal a lymphocytic pleocytosis or may be relatively acellular and may have an elevated protein. Current quantitative HIV RNA PCR on spinal fluid (spinal fluid viral load) is often positive. There should be no evidence of other infection such as CMV. In other words, CMV PCR should be negative. Treatment of vacuolar myelopathy should consist of highly active antiretroviral therapy (HAART) that includes at least two drugs to which the patient's virus is sensitive and that cross into the central nervous system (CNS).

Once the examiner has excluded these more dangerous diagnoses and the patient exhibits the classic history and examination, then the diagnosis of DSPN is easy. It requires a trained examiner, a 128 Hz tuning fork, and a reflex hammer. DSPN is often one of the most difficult and frustrating painful conditions for any healthcare provider to treat. By definition, it is an axonopathy, meaning that the actual distal nerve segments are damaged. The most common causes of DSPN worldwide include diabetes mellitus, alcoholism, and HIV disease. The diagnostic workup for DSPN must include testing for and exclusion of toxic-metabolic abnormalities and neurosyphilis. These tests consist of a B12 level, a folate level, a thyroid panel that includes thyroxin level and thyroid stimulating hormone level (TSH), and syphilis serology. Nerve conduction velocities and electromyography, while confirming the diagnosis, are rarely necessary and are often too painful for the patient with DSPN to endure. When the history reveals exposure to heavy metals such as might be experienced by pesticide workers, lead reclamation workers, industrial and house painters, gardeners and landscapers, and chemists, then urine testing for lead, arsenic, and mercury should be performed. If these are elevated, then chelation therapy is indicated.

In the HIV-infected patient, specific medications are well known to contribute to or directly cause DSPN. These include the drugs commonly called "D" drugs—the nucleoside analogs ddI (Videx®, Bristol-Myers Squibb), ddC (Hivid®, Roche), and d4T (Zerit®, Bristol-Myers Squibb)—and the prophylactic agent against PCP, Dapsone. Other drugs that commonly cause DSPN include vinca alkaloid chemotherapeutic agents such as vincristine and vinblastine, which are often used to treat Kaposi's Sarcoma (KS) and lymphoma, the two main tumors associated with HIV. It may be necessary to reduce the doses of these medications or eliminate them from the treatment regimen when DSPN is severe. It is more likely that the medication or medications known to cause DSPN and that are most temporally related to its symptoms are the cause of the DSPN rather than medications previously tolerated. For example, if a patient has been taking d4T for a relatively

Painful Sensory Neuropathy: A Therapeutic Challenge *(continued)*

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long period of time without symptoms and ddI is added, then ddI is more likely to be the cause of the DSPN and its dose should be lowered or it should be discontinued. When two or more drugs known to cause DSPN are initiated at approximately the same time, then it may be difficult to discern which medication is causing the problem and, in fact, any and all of the medications may be contributing. The decision as to whether or not to lower the dose or discontinue any potentially toxic medication should be based on several factors. These include the importance of the particular medication in treating the condition and how opposed the patient feels to continuing the medication. Often, when the pain is minimal or is being adequately controlled, the patient will adhere to therapy. This is especially true when the medication is working to treat tumors such as Kaposi's Sarcoma or lymphoma or, with regard to HAART, when the patient has achieved undetectable HIV viral load and is feeling well aside from having painful feet.

Treatment Options

Once all of these other entities and contributing factors to DSPN have been considered and addressed—or, in cases where there are no contributing factors apart from HIV itself—the treatment becomes one of best controlling the HIV infection and the chronic pain.

There are many different classes of drugs that neurologists and pain specialists use to treat the chronic pain associated with DSPN. These include antidepressants (primarily tricyclics), anticonvulsants/antiarrhythmtics, and opiates.

The exact choice of a tricyclic antidepressant anti-pain medication should depend on the amount of associated sedation necessary to treat insomnia or anxiety and should include specific indications for the drug. For example, in patients with extreme insomnia, medications that are relatively sedating, such as amitriptyline (Elavil®, AstraZeneca) and sinequan (Doxepin®, Roerig), have marked anticholinergic side effects, which include induction of sleepiness, dry mouth, and occasionally urinary retention and constipation. For those who require some sedation, nortriptyline (Pamelor®, Mallinckrodt) may be beneficial. In those who cannot tolerate the sedating side effects of these medications, desipramine (Norpramine®, Aventis), which has the least anticholinergic side effects of this group, would be indicated. In patients who have panic and anxiety disorder, the use of imipramine (Tofranil®, Mallinckrodt) may be useful to treat both pain and panic. The anticonvulsant carbamazepine (Tegretol®, Novartis) is tricyclic-like in its chemical structure and may also be beneficial in treating painful neuropathy. Carbamazepine is also approved to treat bipolar affective disorder and may be quite useful in bipolar patients with pain. Because carbamazepine has a higher propensity for inducing granulocytopenia (lowering white blood cell count), blood counts must be monitored more carefully during its administration.

The exact dosing of the tricyclic medications is identical across the entire class and usually will begin with 25 mg of a single nighttime dose, which can be advanced over the course of 1 to 2 weeks to 75 mg, as tolerated; dosage may be higher with appropriate drug level monitoring. The dose of carbamazepine starts out at one 200 mg tablet daily; over the course of the first 2 weeks, the dose is advanced to 200 mg three times daily. However, caution is necessary because carbamazepine interacts with ritonavir (Norvir®, GlaxoSmithKline), and the dose of carbamazepine usually has to be reduced by one-half or more in order to avoid serious toxicity. The appropriate response and dosing are monitored by blood levels and cessation or diminution of pain.

For carbamazepine, blood counts should be performed twice weekly for the first 2 weeks and weekly thereafter for the first month; then, if the patient's blood counts are stable, the levels and complete blood counts may be monitored monthly. Therapeutic levels for carbamazepine range from 6–12 mg/dL. In debilitated patients, elderly patients, or patients with history of cardiac arrhythmia, appropriate cardiac clearance should be obtained, which at minimum includes an electrocardiogram to rule out an obvious arrhythmia. In rare instances, the tricyclic medications can induce arrhythmias, which are usually tachy-arrhythmias. Again, significant side effects from tricyclic medications include dry mouth, sedation, and may include urinary retention and constipation. These side effects are usually minimized by the gradual advancement of dose, although dry mouth may be persistent. Patients may be instructed to chew gum or carry hard candies during the day, and to keep a glass of water at the bed stand during the night to alleviate this symptom.

Of the selective serotonin reuptake inhibitors (SSRIs), both paroxetine (Paxil®, GlaxoSmithKline) and nefazodone (Serzone®, Bristol-Myers Squibb) have undergone limited trials for the treatment of chronic pain. They may be useful as adjunct therapy when an activating antidepressant is indicated. Citalopram (Celexa™, Forest Laboratories) in limited series has shown benefit in treating both depression and pain. It is the newest of the approved SSRIs and has limited drug–drug interactions, making it safer to use in patients on HAART.

Perhaps the greatest development in the treatment of pain associated with DSPN has been the introduction of gabapentin (Neurontin®, Parke-Davis). This medication was originally approved by the FDA in the United States for adjunct therapy in specific seizure disorders, and has been more recently approved for the treatment of many severely debilitating neuropathies, including DSPN associated with diabetes and post-herpetic neuralgia (after-shingles pain). While its exact mechanism of action is not entirely understood, gabapentin works to ameliorate pain via a completely independent neurotransmitter pathway known as GABA (Gamma Amino Benzoic Acid). Because gabapentin is metabolized by a separate enzymatic reaction in the liver, it does not interact with any other medications and is therefore very safe. Its main side effect consists of sedation, which usually subsides after an initial 2-week induction phase. The dosing can start as high as one 300 mg capsule three times daily; after 1 week, the dose can be escalated to two 300 mg capsules three times daily. Doses as high as 1,200 mg three times daily have been safely used; in our experience, however, most adults with DSPN respond at somewhere between 300 mg three times daily and 900 mg three times daily. The medication should be taken with food, if possible, to avoid any gastrointestinal upset; because the drug is available in capsules with a strength as low as 100 mg, dose escalation can easily be modified if patients are overly sedated.

Another anticonvulsant in the GABA family currently being studied for painful DSPN is lamotrigine (Lamictal®, GlaxoSmithKline). Its exact mechanism of action is probably similar to that of gabapentin, but specifics remain unknown. The dosing is more tedious because it is more sedating than gabapentin and optimal doses of 100 mg twice daily can take over a month to attain. The standard starting dose is 25 mg twice daily, which is increased by 25 mg at each dose per week. In our experience, when patients fail to respond to gabapentin, they generally will not respond to lamotrigine; however, if they have intolerable side effects to one of these agents, the other agent may still

be beneficial. For both gabapentin and lamotrigine, it is not necessary to monitor drug levels. Nevertheless, for lamotrigine, periodic monitoring of blood counts and serum chemistries is indicated.

The oral anesthetic lidocaine–like drug mexiletine (Mexetil®, Boehringer Ingelheim) has also shown benefit in the treatment of DSPN-associated pain. It is contraindicated in any patient with a known cardiac arrhythmia. Side effects may include anxiety, and it may be beneficial in individuals for whom a stimulant would be helpful. It has been studied extensively in diabetic painful neuropathy and we find it particularly useful in HIV-infected patients who are diabetic. The typical dose is 150 mg taken three times daily; the dose can be escalated as high as 150 mg taken four times daily.

More recently, the lidocaine patch (Lidoderm®, Endo Laboratories) has become available for topical local anaesthetic administration. This is often a useful adjunct in managing pain due to DSPN. These patches may be cut and placed directly upon the painful area, such as the feet. Side effects are limited to local skin irritation and are rare.

The drugs that are currently under some clinical investigation for DSPN are the gabapentin pro-drug (XenoPort Pharmaceuticals), and Prosaptide (Biotechnology General Corporation). Both of these agents have shown efficacy in preliminary experimental trials involving DSPN associated with diabetes.

In patients with severe pain, especially in those that show incomplete response to the above-mentioned agents used alone or in combination, it often is necessary to add a narcotic analgesic. When there is episodic breakthrough pain, a short-acting oral narcotic or narcotic potential medication is the drug of choice; the range of available drugs includes tramadol hydrochloride (Ultram®, Ortho-McNeil), acetaminophen (Tylenol®, McNeil Consumer & Specialty Pharmaceuticals) with codeine, hydrocodone (Vicodin®, Abbott), oxycodone (Percocet®, Endo Pharmaceuticals), and oral hydromorphone (Dilaudid®, Abbott). When multiple dosings of these medications are necessary, longer acting narcotic analgesics become necessary. These include oxycodone (Oxycontin®, Purdue Pharma), morphine sulfate (MS Contin®, Purdue Frederick), or Oramorph, and methadone. When there is considerable gastrointestinal distress and a long-acting narcotic is necessary, Fentanyl (Duragesic®, Janssen) patches are useful. Doses of all narcotic analgesics must be individualized; however, it is important to note that Tylenol® with codeine, Percocet®, Percodan®, Vicodin®, and Loracet® all contain Tylenol®, and the daily maximum of these medications in an average-sized adult is 6 tablets per day due to potential liver toxicity. These medications can be used to treat breakthrough pain in lesser doses in patients who are taking long-acting narcotics or in patients, as stated above, whose pain is only intermittent. However, when a patient requires more than 6 doses of these daily, the patient should be switched to a long-acting narcotic agent that does not contain Tylenol®.

Conclusion

There are some basic principles that any treatment provider must follow when administering to patients with chronic pain. First, remember that pain is entirely subjective and our objective should be to treat the patient and not the healthcare provider. This means that narcotic analgesics can be used safely when there is a clear diagnosis such as DSPN; to allow the patient the best quality of life, healthcare providers should not be frightened or biased against ameliorating the patient's pain. Second, the healthcare provider should avoid inappropriate use of any pain management intervention. For example, an intervention is unnecessary if the desired objective can be achieved by simpler means. To illustrate this, a long-acting narcotic such as MS Contin® may not be necessary if the patient has not undergone a trial of Neurontin®. If a pain-management intervention is unsuccessful—for example, if the medication is not treating the pain adequately or is causing intolerable side effects—then an alternative intervention must be entertained. Whenever complications or side effects outweigh a treatment benefit, the treatment should be discontinued and a different treatment should be undertaken. Certainly, when quality of life is diminished because of the therapeutic intervention, other forms of treatment must be considered.

When managing patients with chronic pain who require narcotic analgesics and who may be taking benzodiazepines such as clonazepam (Klonopin®, Roche) it is often helpful to discuss and insist upon what is known as the "Verbal Pain Contract." This contract places several responsibilities on the patient. The standard Verbal Pain Contract includes the following mandates:

1. Only take what your doctor prescribes. Do not obtain pain medications from any other physician or source.
2. Try to use only one pharmacy.
3. Do not lose your medication or have it stolen.
4. Do not buy pain medication or sell your prescribed medication on the street.
5. If the medication is not controlling your pain, tell your doctor and ask for an increase in dose.
6. As a courtesy, if you require more medication, call your doctor at least one week in advance for refills and to schedule an earlier appointment to avoid pain, anxiety, and possible drug withdrawal.
7. Above all, be honest. Your doctor cannot help you if you do not communicate your needs effectively.

The goal for most patients with painful DSPN is to attain the highest quality of life while remaining functional with regard to activities of daily living. Using various combinations of the treatment modalities discussed in this article usually results in adequate pain control. A realistic goal is to tell patients that pain control may not be complete, but that, at least from a starting point, pain should not be the central focus of every waking minute. Over time, with multiple therapies, their lives should be pain-controlled and fulfilling.

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Editor's Note: See also the article Assessment of Cognitive Changes in HIV/AIDS by Jeanne K Kemppainen in the Quality of Life section of this issue.

STD Update

RICHARD S FERRI, PHD, ANP, ACRN, FAAN

STDs Are Increasing the Rate of HIV Infection

The rates of certain sexually transmitted diseases (STDs) are on the rise. There are approximately 5 million new cases of *Trichomonas vaginalis* in the United States annually. Researchers believe that infection with *T. vaginalis* is an emerging factor in amplifying HIV transmission in both HIV-positive and -negative individuals. The shedding of HIV is increased in HIV-positive people co-infected with *T. vaginalis*. In HIV-negative people, the potential portal of entry for HIV may be increased twofold in the presence of *T. vaginalis* due to a breakdown of mucosal integrity. In addition, since most individuals infected with *T. vaginalis* have little or no clinical symptoms, they may remain sexually active while infected.[1]

"Party Drugs" and Unsafe Sex

Increased use of recreational or "party drugs" such as ecstasy, "poppers," and methamphetamines ("crystal meth") also influences unsafe sexual behaviors in HIV-positive gay and bisexual men.[2] The popularity of these recreational drugs has been on the rise, especially among younger adults who may not see themselves as being vulnerable to infection.

(Editor's Note: Please see "Risky Cocktails" in this issue for additional information.)

STD/HIV Screening in Men Who Have Sex with Men

The Centers for Disease Control and Prevention is now recommending that all gay or bisexual men ("men who have sex with men") be screened annually for a variety of STDs including infection with HIV. Vaccination against hepatitis A and B is also recommended.[3]

Urine Testing for HIV and Other STDs

The Food and Drug Administration (FDA) has approved a urine test for detection of *Neisseria gonorrhoeae* (gonorrhea) DNA, and *Chlamydia trachomatis* (chlamydia) DNA. The test is highly accurate and reliable, and results can be returned in just 4 business days. Also, the price of the test is competitive, and it can be used at facilities that have limited laboratory services.

Urine testing is also painless and noninvasive compared to blood and urogenital sampling. This noninvasive method may encourage people to get tested and reduces the need for skilled phlebotomists and clinicians.[4] There are over 400,000 needle stick injuries reported every year in the United States alone. Urine testing has the potential to reduce this number and thus to reduce occupational acquisition of HIV.[5]

The AMPLICOR® CT/NG Test by Roche allows for screening of the two STDs with one simple sample. More information is available online at: www.roche-diagnostics.com /ba_rmd/rmd_products_womens_health11.html.

STDs: The Other Hidden Epidemic

The actual rate of undiagnosed and untreated infection with *Neisseria gonorrhoeae* and *Chlamydia trachomatis* remains elusive, but researchers have long suspected that the rate is high because many individuals with these infections are asymptomatic.

Adults (n = 579) in Baltimore age 18 to 35 underwent a urine screen for these STDs.[6] An estimated 5.3 percent of that population had an untreated gonococcal infection, and 3.0 percent were estimated to have had an untreated chlamydial infection. Very few of the participants in the study reported any urogenital symptoms over the 6 months prior to the study.

Neisseria gonorrhoeae and *Chlamydia trachomatis* infections can lead to a wide variety of other reproductive health issues, such as pelvic disease, and may increase the likelihood of HIV transmission.

In the Baltimore study the number of untreated infections was greater than the number of actual infections diagnosed and treated during the same time period.

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DRUG	INDICATION	DOSE	CONSIDERATIONS
Flagyl® (metronidazole) (metronidazole gel) Pfizer Pharmaceuticals Patient Support: www.pfizer.com **Clindamycin cream** Pfizer Pharmaceuticals Patient Support: www.pfizer.com	Bacterial vaginosis (BV)	500 mg orally 2x/day for 7 days (0.75%) One full applicator (5 g) intravaginally daily for 5 days (2%) One 5 g applicator intravaginally at bedtime for 7 days	Oil-based creams and suppositories may weaken latex condoms and diaphragms. Avoid alcohol for 24 hours following metronidazole. *Pregnant Women:* Metronidazole 250 mg orally 3x/day for 7 days OR clindamycin 300 mg orally 2x/day for 7 days Existing data do not support the use of topical (intravaginal) preparations during pregnancy.
Zovirax® (acyclovir) GlaxoSmithKline Patient Support: www.gsk.com **Famvir®** (famciclovir) Novartis Patient Support: www.famvir.com **Valtrex®** (valacyclovir) GlaxoSmithKline Patient Support: www.valtrex.com	Genital herpes simplex	First clinical episode of genital herpes: Acyclovir 400 mg orally 3x/day for 7 to 10 days OR acyclovir 200 mg orally 5x/day for 7 to 10 days OR famciclovir 250 mg orally 3x/day for 7 to 10 days OR valacyclovir 1 g orally 2x/day for 7 to 10 days	Treatment may be extended if healing is incomplete after 10 days of therapy. For treatment during pregnancy, see the CDC Treatment Guidelines. The safety of acyclovir and valacyclovir during pregnancy has not been established.
Zithromax® (azithromycin) Pfizer Pharmaceuticals Patient Support: www.zithromax.com **Doxycycline** Patient Support: www.doxycycline.com	Chlamydial infection	Adults or Adolescents >45 kg with uncomplicated infection of the cervix, urethra, or rectum. Azithromycin 1 g orally in a single dose OR Doxycycline 100 mg orally 2x/day for 7 days	Clinicians should consider advising all women with chlamydial infection to be rescreened 3 to 4 months after treatment, to rule out subsequent re-infection. Clinicians are also strongly encouraged to rescreen all women treated for chlamydial infection when they next present for care within the following 12 months.

Editor's Note: Providers are reminded that STD screening and treatment is an opportunity for HIV antibody testing for patients who have never been tested or who tested negative in the past.

References: 2002 CDC Guidelines for Management of Sexually Transmitted Diseases: www.cdc.gov/STD/treatment/TOC2002TG.htm
CDC Division of STDs: www.cdc.gov/STD/Phone: 800 227 8922 | American Sexual Health Association: www.ashastd.org/

The information contained herein is not intended to be a substitute for professional medical advice. You should not use this information to diagnose or treat a health problem or disease without consulting with a qualified healthcare provider. Please consult your healthcare provider with any questions or concerns you may have regarding your condition.

The Dual Epidemic: Screening and Diagnosing TB in HIV-Infected Persons

JANICE BOUTOTTE, MS, RN, CS

Many people think tuberculosis (TB) is a disease of the past. However, despite declining TB disease case rates in the United States, it remains a serious threat for HIV-infected persons.[1] Worldwide, TB is the most common opportunistic disease in persons with HIV infection, appearing early in the disease process. One-third of the world's population (two billion people) is infected with *Mycobacterium tuberculosis* (M. tb): an estimated eight million people develop TB each year, and two million die every year from TB; the disease accounts for 7 percent of all deaths and more than 25 percent of preventable deaths. The highest TB incidence and case fatality rates are in African countries with high HIV infection rates.[2] In fact, worldwide, TB is responsible for the death of one in three people living with HIV/AIDS, making it the leading cause of death among people infected with HIV.[1]

Worldwide, the prevalence of resistance to at least one TB drug is as high as 37 percent; for multidrug-resistant TB (MDRTB), resistance prevalence is up to 14 percent.[3] In the United States, the CDC has reported that the risk of drug-resistant TB, including MDRTB, was even higher among HIV-infected individuals, compared to others.[1]

Co-Pathogenicity of TB/HIV Disease

In most TB-infected persons, the body's immune system keeps the bacteria in check. Without treatment, an individual with latent TB infection (LTBI) has a 5 to 10 percent lifetime risk of developing clinically apparent TB disease. However, persons co-infected with HIV have a 7 to 10 percent annual risk of developing TB disease, and a lifetime risk up to 800 times higher than someone without HIV infection.[4,5]

HIV attacks and destroys the lymphocytes responsible for cell-mediated immunity. In persons who have HIV infection and subsequently acquire TB infection, T-cells are unable to mediate walling off of TB organisms. HIV-infected persons with impaired cell-mediated immunity who subsequently acquire TB infection develop TB disease rapidly: up to 50 percent of such persons may do so within 2 years after TB infection. Rapid progression of primary infection to infectious TB amplifies the spread of the strains of M. tb that are prevalent in the community, including multidrug resistant strains.[5]

Active TB disease also appears to accelerate the course of HIV disease. Co-infection is associated with a higher plasma virus load than is found in CD4 count–matched HIV-infected controls; it is also associated with an accelerated rate of decline in CD4 count. Moreover, the virus load increases during the course of treatment of TB.[5]

Diagnosis of TB in the HIV-Infected Individual

Early diagnosis and effective treatment of TB among HIV-infected individuals can minimize the negative effects of TB on the course of HIV, can cure TB, and can interrupt the transmission of TB to others, especially other immunocompromised persons.[1] The tuberculin skin test (TST) is the standard method used to diagnose LTBI.[4] HIV-infected persons may have a compromised ability to react to TSTs because of cutaneous anergy associated with progressive immunosuppression, but they should still be tested at least annually.[6] Effective treatment of HIV infection often reverses the immune suppression that causes anergy. The Centers for Disease Control and Prevention (CDC) recommend testing HIV-infected persons for TB as soon as possible after diagnosis of HIV infection, and also after a potential TB exposure.[1]

TB infection produces a delayed-type hypersensitivity reaction to tuberculin purified protein derivative (PPD), an extract of culture filtrate isolated from M. tb. The TST employs PPD injected into the skin and follow-up assessment of any subsequent induration (the manifestation of a delayed-type hypersensitivity reaction). Interpretation and classification of the TST are based on the sensitivity and specificity of the TST and the prevalence of TB infection in different groups. In HIV-infected persons, the lowest criterion cut-point for the size of a positive reaction (highest sensitivity) is used to help ensure that those at highest risk for developing active TB are identified and receive treatment. Thus, induration of >5 mm is considered a positive reaction. Skin testing with nontuberculous antigens (anergy testing) has not been standardized, results have not been reproducible, and preventive treatment given to anergic HIV-infected persons is not useful. The usefulness of anergy testing in selecting tuberculin-negative, HIV-infected persons who might benefit from treatment of LTBI has not been demonstrated and is no longer recommended for routine use.[6]

HIV infection also alters the clinical presentation of TB disease, with less cavitary disease and more atypical, disseminated, and extrapulmonary manifestations. The typical signs and symptoms of pulmonary TB are cough, fever, night sweats, weight loss, and upper-lobe infiltrates on chest radiographs, with or without cavitation. TB in an immunocompromised host can be associated with atypical symptoms, a lack of typical symptoms, and a paucity of findings on chest radiographs.[1]

In non-immunocompromised adults with "classic" pulmonary TB, chest radiographic abnormalities often occur in the apical and posterior segments of the upper lobe or in the superior segments of the lower lobe. Infiltrates and cavities suggest reactivation of LTBI. However, lesions may appear anywhere in the lungs and vary in size, shape, density, and cavitation, especially in HIV-infected and other immunosuppressed persons. A negative chest radiograph usually rules out pulmonary disease, but does not eliminate the possibility of active disease in other organs. However, a normal chest x-ray is possible with active pulmonary TB in HIV-infected persons.[4] In addition, the diagnosis of TB in HIV-infected persons can be further complicated by the presence of other pulmonary opportunistic infections, such as *Pneumocystis carinii* pneumonia and *Mycobacterium avium* complex disease, and by the occurrence of TB in extrapulmonary sites.[1]

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DRUG	DAILY ADULT DOSE	TWICE WEEKLY ADULT DOSE	POTENTIAL SIDE EFFECTS/OTHER CONSIDERATION(S)
Ethambutol	15–25 mg/kg	50 mg/kg	Optic neuritis, decreased visual acuity and red-green color discrimination, skin Dura rash.
Isoniazid (INH)	5 mg/kg Max. 300 mg	15 mg/kg Max. 900 mg	Hepatotoxicity, hepatitis, peripheral neuropathy, flu-like syndrome, hypersensitivity. Should be given with pyridoxine 50 mg with each dose.
Pyrazinamide (PZA)	15–30 mg/kg Max. 2 grams	50–70 mg/kg Max. 4 grams	Hepatotoxicity, hyperuricemia, arthralgias, skin rash, gastrointestinal irritation.
Rifabutin*	300 mg daily		Fever, headache, flu-like syndrome, GI symptoms, decreases AZT serum levels.
Rifampin Aventis Pharmaceuticals Patient Support: 800-981-2491	10 mg/kg Max. 600 mg	10 mg/kg Max. 600 mg	Orange discoloration of urine and other secretions, nausea, vomiting, hepatitis, fever, purpura (rare). Reduces levels of many drugs: PIs, NNRTIs, birth control, methadone, warfarin, and theophylline.

*Used as an alternative to rifampin for persons on PI or NNRTI therapy. Check recommendations for PIs and NNRTIs.[6]

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Treatment Planning to Maintain Good Outcomes

BILL VALENTI, MD

Structured Treatment Interruption (STI) is not ready for prime time, according to the US Department of Health and Human Services guidelines for HIV treatment. Many of our patients have treatment interruptions or regimen changes for a variety of reasons, including treatment failure, management of adverse events, and adherence problems.

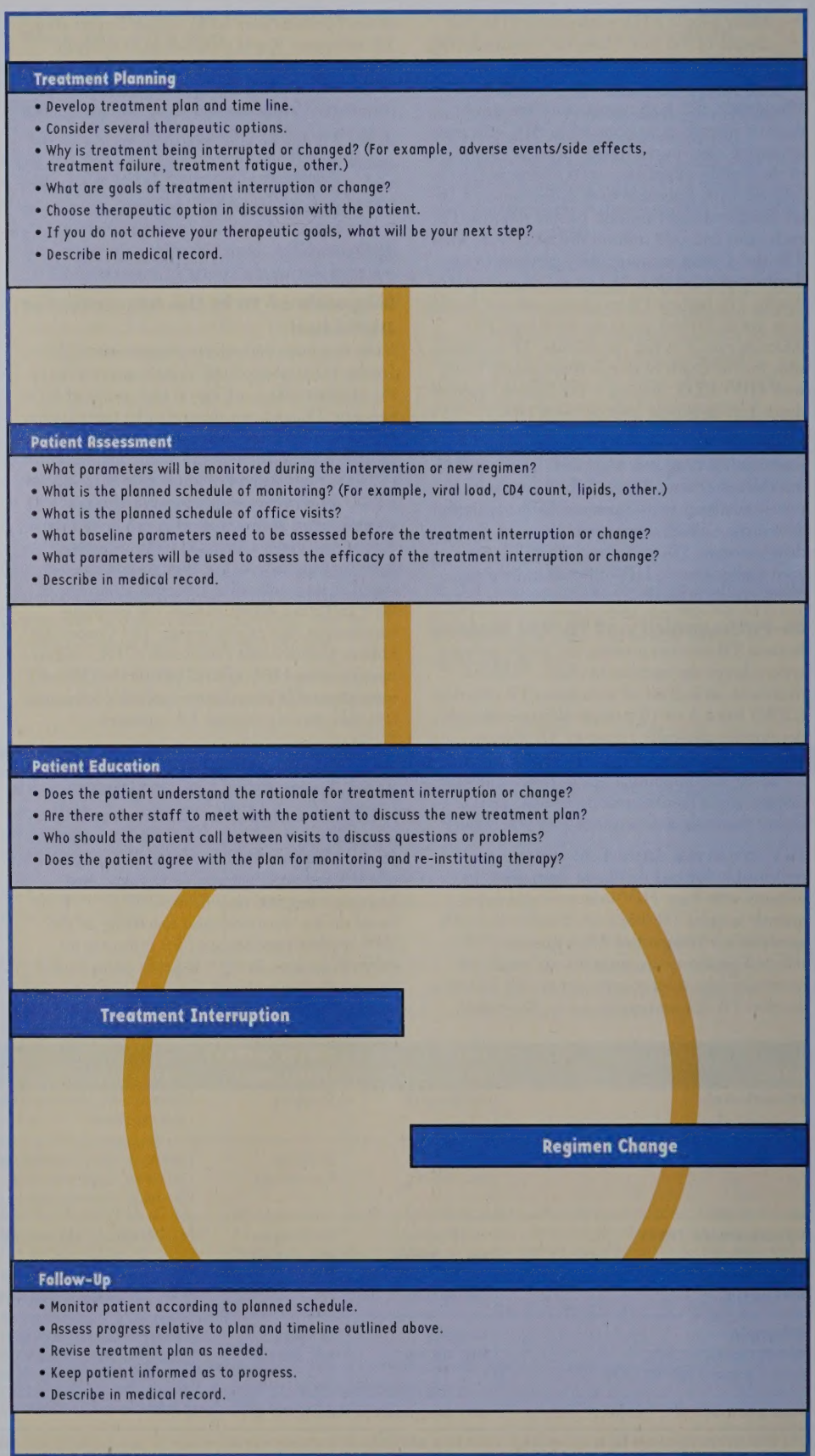
The treatment algorithm at the right emphasizes an individualized, multidisciplinary approach to planning when changing or interrupting treatment. This approach includes a strong patient–provider communication component.

Some considerations include an agreement between the patient and provider that treatment-plan revisions require close follow-up for clinical and laboratory parameters on a predetermined schedule. This new treatment plan should be written in the medical record and should outline the goals of the regimen change or interruption, frequency of visits and laboratory monitoring, the threshold for restarting therapy, and any anticipated changes in the drug regimen when treatment is restarted.

In many cases, the patient may need to be monitored more frequently depending on the rationale for interrupting or changing therapy. For example, the provider and patient may agree that viral load may need to be monitored monthly while off therapy, in contrast to quarterly monitoring during treatment in the patient whose viral load is fully suppressed.

A proactive approach to changes in treatment can help maximize both adherence to the revised treatment plan and good patient outcomes.

See Dr Valenti's bio on page 11. N


Treatment Planning
• Develop treatment plan and time line.
• Consider several therapeutic options.
• Why is treatment being interrupted or changed? (For example, adverse events/side effects, treatment failure, treatment fatigue, other.)
• What are goals of treatment interruption or change?
• Choose therapeutic option in discussion with the patient.
• If you do not achieve your therapeutic goals, what will be your next step?
• Describe in medical record.
Patient Assessment
• What parameters will be monitored during the intervention or new regimen?
• What is the planned schedule of monitoring? (For example, viral load, CD4 count, lipids, other.)
• What is the planned schedule of office visits?
• What baseline parameters need to be assessed before the treatment interruption or change?
• What parameters will be used to assess the efficacy of the treatment interruption or change?
• Describe in medical record.
Patient Education
• Does the patient understand the rationale for treatment interruption or change?
• Are there other staff to meet with the patient to discuss the new treatment plan?
• Who should the patient call between visits to discuss questions or problems?
• Does the patient agree with the plan for monitoring and re-instituting therapy?
Treatment Interruption
Regimen Change
Follow-Up
• Monitor patient according to planned schedule.
• Assess progress relative to plan and timeline outlined above.
• Revise treatment plan as needed.
• Keep patient informed as to progress.
• Describe in medical record.

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Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents. Latest revision August 8, 2002. Available at: www.aidsinfo.nih.gov/

Update to Guidelines and Recommendations

BILL VALENTI, MD

Smallpox Vaccination and HIV

Redfield RR, Wright DC, James WD, et al. Disseminated vaccinia in a military recruit with human immunodeficiency virus (HIV) disease.
N Engl J Med. 1987;316:673–676.

Recently, the Centers for Disease Control and Prevention (CDC) published new recommendations about the use of smallpox vaccine. These guidelines are updated regularly, and readers are advised to monitor the Internet sites listed below for the most recent updates.

Smallpox vaccine is made from the vaccinia virus, which is a "pox"-type virus related to smallpox. The smallpox vaccine contains the "live" vaccinia virus, not dead virus like many other vaccines.

The vaccinia (smallpox) vaccine may cause severe complications, including eczema vaccinatum, progressive vaccinia, and postvaccina encephalitis. People with compromised immune systems, or those living with such people, are at greater risk for serious side effects from the smallpox vaccine. HIV-positive individuals, transplant recipients, cancer patients, individuals with other immune deficiency disorders—and pregnant women—should not get the smallpox vaccine unless they have been exposed to the smallpox virus.

Complications are more common in immunosuppressed patients and may be fatal. The only case report in the literature is of a 19-year-old military recruit who was found to be HIV-positive only after he developed disseminated vaccinia after smallpox vaccination.

The risk in these individuals is not only from vaccination, but also from direct contact with individuals who were recently vaccinated. The pustule that forms at the site of vaccination may be the source of spread of the virus to immunosuppressed individuals, even if they were not vaccinated.

The CDC guidelines discuss HIV testing prior to vaccination in people who do not know their HIV status. Before vaccination, potential vaccinees should be educated about the risk of vaccine complications among persons with HIV infection or other immunosuppressive conditions. Persons who think they may have one of these conditions should not be vaccinated.

The CDC does not recommend mandatory HIV testing prior to smallpox vaccination. Instead, HIV testing should be readily available to all persons considering vaccination. People with a history of a risk factor for HIV infection and those who are not sure of their HIV status should be tested. Because known risk factors cannot be identified for some persons with HIV infection, anyone who is concerned that they could have HIV infection should be tested prior to vaccination.

In the meantime, studies are awaiting US Food and Drug Administration approval to test a new smallpox vaccine that will measure side effects and immune response in people with AIDS. If results are favorable, millions of immune-compromised individuals could be vaccinated against smallpox.

The most recent smallpox vaccine updates can be obtained at:

www.bt.cdc.gov/agent/smallpox/vaccination/acip-recs-oct2002.asp

www.bt.cdc.gov/agent/smallpox/vaccination/acip-guidelines.asp

www.bt.cdc.gov/agent/smallpox/index.asp

Antiretroviral Use in Pregnancy

Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. N Engl J Med. 1994;331(18):1173–1180.

US Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1–Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States—Summary. MMWR. November 22, 2002;51(RR18):1–38

Recently, the CDC updated their recommendations for antiretrovirals in pregnant women. The key points of these revised recommendations are:

- AZT (Retrovir®; GlaxoSmithKline) should be included in the regimen according to the Pediatric AIDS Clinical Trials Group Study 076 regimen unless the woman cannot tolerate AZT.
- Plasma viral load levels should be monitored during pregnancy according to the guidelines for management of HIV-1-infected adults. The most recently determined viral load value should be used when counseling a woman about mode of delivery.
- Perinatal HIV-1 transmission is reduced by scheduled cesarean section among women with unknown viral load levels who are not receiving antiretroviral therapy or AZT for prevention of perinatal transmission
- Women with viral load levels >1,000 copies/mL should be counseled regarding the benefit of scheduled cesarean delivery in reducing the risk of vertical transmission.
- Data are insufficient to evaluate the potential benefit of cesarean section for neonates of antiretroviral-treated women with plasma viral load levels below 1,000 copies/mL.
- Women should be informed about the risks associated with cesarean delivery, and these risks to the woman should be balanced with potential benefits expected for the neonate.

The guidelines are equivocal about resistance testing in pregnancy, but note that the International AIDS Society–USA and EuroGuidelines Group for HIV-1 Resistance recommend that all pregnant women with detectable viral load levels undergo resistance testing, even if antiretroviral-naïve, to maximize the response to antiretroviral drugs in pregnancy.

Editor's Note: See the discussion of the safety of antiretrovirals in pregnancy elsewhere this issue.

More information can be obtained at:

www.cdc.gov/mmwr/preview/mmwrhtml/rr5118a1.htm

www.aidsinfo.nih.gov.

Federal Guidelines Web Sites

Reorganized

The HIV/AIDS Clinical Trials Information Service (ACTIS) and its sister service, the HIV/AIDS Treatment Information Service (ATIS), have merged into AIDSinfo. AIDSinfo provides all of the information that was available from ACTIS and ATIS, including treatment guidelines, a summary of HIV drugs, and sections on HIV vaccines, clinical trials, HIV education, and other resources. Databases are also downloadable to personal digital assistants (PDAs).

More information can be obtained at:
www.aidsinfo.nih.gov/

See Dr Valenti's bio on page 11.

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remaining product. Abbott also advised the laboratories to contact the healthcare providers served by their facility and have them determine if their patients need to be retested. The physician should offer a retest to the patients whose test results were negative and who were not already treated. Repeat testing should be performed on a fresh specimen and not on retained specimens. Abbott Labs will reimburse expenses associated with repeat testing.

Abbott voluntarily recalled 32 lots of its gonorrhea test kits after learning through routine internal testing that certain lots did not meet specifications and, as a result, could report positive test results as negative. Upon further testing, Abbott determined that only 16 of these 32 lots did not meet internal release criteria. Abbott is continuing to investigate the cause of the problem.

The 16 lots that failed to meet specification when tested by Abbott are: 84073M400; 84075M400; 84142M300; 84146M300; 85487M200; 87007M400; 87103M400; 87243M100; 87377M200; 87899M200; 87905M200; 88097M300; 88105M300; 88107M300; 88439M200; and 88439M201.

Patients who received a negative test result with test kits from these lots may need to be re-tested. Approximately 750,000 tests are affected.

Consumers or laboratories with questions can contact Abbott Laboratories at 1-800-527-1869. Physicians with questions on this recall should contact Abbott Laboratories at 1-866-233-0471. N

Source:
http://www.fda.gov/bbs/topics/NEWS/2002/NEW00832.html. Date Accessed: December 02, 2002

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always be administered in combination with other antiretroviral agents.

Average wholesale price (AWP) is a useful index for comparing drug prices. AWP is the average of prices charged by the national drug wholesalers for a given product. The operative word is average. AWP was developed to provide a price that all parties could agree upon to make electronic processing possible. AWP is different than the manufacturer's suggested wholesale price (SWP) and will likely differ from the retail price, which is usually determined by third-party payers.

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- van Leth1 F, et al. Lipid changes in a randomized comparative trial of first line antiretroviral therapy with regimens containing either nevirapine (NVP) alone, efavirenz alone, or both drugs combined, together with stavudine and lamivudine (2NN Study). Abstracts of the 10th Conference on Retroviruses and Opportunistic Infections. February 10–14, 2003. Boston, MA. Available online at: www.retroconference.org. [Abstract 752]
- American Society of Consultant Pharmacists for AWP Information www.ascp.com/public/ga/awp/awpinfo.shtml.

CONTINUED FROM ANEMIA 70

4. With severe anemia, epoetin alpha should be started along with transfusion therapy. This may help reduce or eliminate any additional units of red blood cells. Transfusions in HIV disease have been associated with:
   - Increased risk of death
   - Increased HIV-1 disease progression
   - Increased risk of CMV and other opportunistic infections
   - Increased incidence of allergic reactions
   - Increased incidence of graft-versus-host disease
   - Potential for immunosuppression
     - Increased suppressor T-cell number
     - Decreased natural killer cell activity
     - Decreased helper T-cell/suppressor T-cell ratio
   - Iron and circulatory overload
   - Febrile nonhemolytic transfusion reaction
5. Zidovudine (Retrovir®)–containing regimens are not always the cause of anemia in HIV disease.

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More information about parvovirus can be obtained at: www.cdc.gov/ncidod/diseases/parvovirus/B19.htm. [Accessed 12.22.02]

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phosphate ester pro-drug of the currently available protease inhibitor amprenavir (Agenerase®; GlaxoSmithKline).

This open-label, multicenter study evaluated the safety and efficacy of once-daily dosing of 908 boosted with once-daily ritonavir (908/r) in antiretroviral therapy–naïve patients versus twice daily nelfinavir (NFV—Viracept®; Agouron).

In this study, 660 patients (649 treated) were randomized to receive either 1400 mg of 908 daily combined with low-dose ritonavir (200 mg once-daily) or 1250 mg of nelfinavir (NFV) twice daily. Both groups took the medications in combination with nucleoside analog reverse transcriptase inhibitors 300 mg twice daily of abacavir (ABC—Ziagen®, GlaxoSmithKline) and 150 mg twice daily of 3TC (Epivir®, GlaxoSmithKline).

In the 908/r once-daily arm, 68 percent of 322 patients achieved viral suppression (<400 copies/mL), compared to 65 percent of 327 patients in the NFV arm. Virologic failure at 48 weeks was seen in 4 percent of patients taking 908/r once daily, and in 15 percent of those taking NFV twice daily. Furthermore, a viral load below 50 copies/mL was achieved in 56 percent of patients taking 908/r once daily compared to 52 percent of patients taking NFV twice daily.

Neither group showed any significant increase in cholesterol, triglycerides, or glucose levels.

These results demonstrated the potency, durability, and tolerability of 908/r dosed with four pills once daily (2 pills each of 908 and ritonavir) in therapy-naïve patients. The investigators noted that currently approved protease inhibitors require at least 6 pills a day, and that 908/r offers an adherence advantage.

Schurmann D, Gathe J, Sanne I, et al. Efficacy and safety of GW 433908/r once daily in therapy-naïve subjects, 48 week results, the SOLO Study. Abstracts of the 6th International Congress on Drug Therapy in HIV Infection; Glasgow, UK; November 17–21, 2002. [Abstract PL-14.4]

Editor's Note: Quantitative plasma HIV-1 RNA in both studies used the Amplicor HIV-1 MONITOR Test® Version 1.5 (Roche).

See Dr Valenti's bio on page 11. N

Editor's Note: For updates on atazanavir and GW433908, see the following abstracts of presentations delivered at the 10th Conference on Retroviruses and Opportunistic Infections, Boston, MA., February 10–14, 2003, available online at: www.retroconference.org

- Murphy R, et al. Long-term efficacy and safety of atazanavir with stavudine and lamivudine in patients previously treated with nelfinavir or ATV: 108-week results of BMS Study 008/044. [Abstract 555]
- Nadler J, et al. The NEAT study: GW433908 efficacy and safety in ART-naïve subjects: final 48-week analysis. [Abstract 177]
- DeJesus E, et al. The context study: efficacy and safety of GW433908/RTV in PI-experienced subjects with virological failure (24-week results). [Abstract 178]

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ners. Then restricting the time frame for unsafe sexual practices from 30 days/month to 1–2 days/month during ovulation can significantly reduce the overall risk for HIV transmission to an uninfected partner. Keeping menstrual calendars and recording basal body temperature for at least 3 months can help identify periods of ovulation. Postexposure prophylaxis may be a further means of reducing the risk of HIV transmission to the uninfected partner, as is done with artificial insemination.[21] Men and women considering pregnancy should know that HIV transmission rates are lower with higher CD4 lymphocyte cells, especially when they are above 200.

Safer sex must be encouraged during nonfertile times and patients must be on ART with undetectable viral loads. Treatment of sexually transmitted diseases (STDs) is imperative, because STDs can increase HIV transmission 3 to 10 fold.[22]

Infertility issues related to HIV can complicate a woman's desire for pregnancy. HIV increases spontaneous abortions, stillbirths, and preterm delivery if the mother is not on antiretroviral therapy.[23,24] There is an increased incidence and severity of pelvic inflammatory disease with HIV (6.7–22%), causing blocked fallopian tubes. Substance abuse/use (marijuana, cocaine, heroine, methadone, alcohol, and central nervous system agents such as barbiturates and PCP) can disrupt the hypothalamic–pituitary–ovarian (HPO) axis, altering fertility at various levels.[25] Chemical toxins such as those found in plastics manufacturing, farming, and lead smelters can also alter the HPO, altering fertility.[26] HIV-infected partners may have decreased sperm count or impaired sperm motility, especially if CD4 cell count is less than 200.[27,28]

To keep unborn babies and the uninfected partner safe, it is imperative that patients and healthcare providers communicate about possible desired pregnancies. Mutual participation among patients, their HIV specialists, and their obstetrical specialists will increase positive outcomes, including reduced HIV transmission.

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See Dr Valenti's bio on page 11.

CONTINUED FROM NUCLEOSIDE ANALOGUES 63

One apparent difference between the two drugs is the slower development of resistance with emtricitabine, presumably due to its longer half life. In clinical studies of emtricitabine, the most common adverse events observed have been mild to moderate central nervous system symptoms, diarrhea, headache, nausea, and rash.

These data suggest that switching to a once-daily, PI-sparing antiretroviral regimen including emtricitabine is effective in maintaining suppression of HIV infection, according to the research team. While both arms of the study demonstrated comparable and durable antiviral response, the data may be of particular interest to physicians and patients who may want to consider the option of a convenient once-daily HAART regimen with a low pill burden. In this study, the pill burden for the entire regimen was three pills once daily.

A new drug application for emtricitabine 200 mg once daily was submitted to the FDA in 2002. Approval is anticipated in 2003.

See Dr Valenti's bio on page 11.

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CONTINUED FROM STD UPDATE 90

CDC Recommends Routine HIV Testing

The Centers for Disease Control and Prevention (CDC) believes that the rate of newly HIV infected persons is on the increase due to recent outbreaks of primary and secondary syphilis among men who have sex with men (MSM) and among heterosexuals.

There are over 800,000 people living with HIV in the United States. However, nearly 200,000 of them do not know they are HIV-positive. Placing an emphasis on case finding rather than on the traditional approach of prevention may decrease new infections, the CDC announced. In addition the recent approval of the rapid 20-minute HIV test can expand testing efforts to non-medical sites such as homeless shelters and prisons.

The CDC is also recommending that all pregnant women be tested unless they specifically refuse.

The other major components of the CDC's HIV-testing initiative are to offer HIV testing as part of the regular medical appointment in areas with a high prevalence of HIV and to trace partners of those found to be HIV-infected and to offer them testing and prevention training.

For the complete CDC recommendations please visit:
www.cdc.gov/mmwr/preview/mmwrhtml/mm5215a1.htm

See Dr Ferri's bio on page 94.

Editor's Note: Please see the related editorial on rapid HIV testing located elsewhere in this issue.

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In a study of men with HIV (n = 45), McCain and colleagues examined the effect of a stress-management program on factors related to chronic illness such as psychological distress, quality of life, coping patterns, CD4 lymphocyte count, and illness-related uncertainty.[11] After 6 weeks in the program, participants expressed an improved quality of life and emotional sense of well-being. At 6 months, there was still a decline in HIV-related intrusive thinking. The authors concluded that the use of stress-reduction techniques may have moderated psychological distress over time.

In another study focusing on the effect of stress in HIV disease, Leserman and colleagues examined the effect of stress, depressive symptoms, and social support on the progression of HIV disease.[12] They followed a cohort of 82 gay men over 5.5 years as part of the Coping in Illness Project. Using Cox regression models, they determined that progression to AIDS was positively associated with more cumulative stressful life events (p = .008) and less social support (p =.0002) after controlling for demographic differences, use of tobacco, CD4 count at baseline, and number of antiretroviral medications. In a later study by the same group, progression to AIDS was positively associated with greater life stress, coping by means of denial, and higher cortisol levels, as well as lower life satisfaction and social support scores.[13]

There are many stress-reduction exercises in vogue today. Despite differences in technique, they share a common goal, to restore the body to a state of maximum well-being. The most effective technique varies from person to person and primarily depends on the psychological makeup of the individual. Some examples of simple exercises that can make a difference in your daily stress level are listed in Table 1.

There are many other stress-reducing techniques that professionals employ today. Reiki, therapeutic massage, and reflexology have all been shown to promote an overall sense of well-being and to reduce anxiety levels. Attending structured programs of relaxation exercises and sessions on building coping skills can help patients develop expertise in the ability to adapt to stressful events. Hypnosis, the induction of a deep state of relaxation, allows the introduction of suggestions aimed at changing behaviors or relieving symptoms.

Although all of us must face the challenges of managing stress and the symptoms that accompany it, simple techniques or professional interventions are available to help us achieve a greater quality of life and sense of well-being. The key is taking the time to take care of ourselves and those we care for.

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Clinical Role of Tenofovir

Tenofovir appears to be a potent anti-HIV medication with delayed resistance, low toxicity, and convenient dosing. Initial clinical testing demonstrates that it is an important component in new salvage regimes and in treatment-experienced patients. Only time and clinical experience will determine whether this drug can be used effectively in the antiretroviral-naïve patient and what long-term effects this drug can have on the person infected with HIV.

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See Dr Valenti's bio on page 11. N

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cerebral toxoplasmosis, and extrapulmonary cryptococcosis in patients receiving HAART. In this trial, recurrent infections were seen in patients who only had marginal increases in CD4 cell count at the time they discontinued therapy.[18] Prospective randomized trials to address discontinuation of prophylaxis may not be feasible in the HAART era, given the low incidence of OIs and difficulty recruiting large numbers of subjects.

Patients who discontinue maintenance therapy for OIs require close monitoring because the minimum duration of therapy is not well established, particularly for disseminated MAC. In addition, atypical presentations of this infection have been described among patients who discontinue therapy during HAART.[19,20] Patients who discontinue maintenance therapy for CMV retinitis should have monitoring ophthalmologic exams as part of their follow-up.

Discontinuing prophylaxis for OIs has many advantages. It reduces cost, decreases pill burden, and thus may facilitate adherence. It also reduces the potential for adverse events and drug interactions. However, discontinuing prophylaxis for OIs should be decided on a case-by-case basis, taking into account the likelihood of continued adherence for sustained immunologic response to HAART. Prophylaxis should be reinstituted if CD4 counts decline to levels that signify risk for opportunistic infection.

Table 1 summarizes the recommendations of the NYS DOH AIDS Institute Criteria for the Medical Care of Adults with HIV infection. It is based on the current guidelines and expert opinion.[20]

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Internet Resources

- HIV Resistance Web
  www.HIVresistanceWeb.com/
- HIV InSite
  http://hivinsite.ucsf.edu/InSite.jsp?page=kb-02-02-03

CONTINUED FROM TUBERCULOSIS 91

Treatment of Latent TB Infection or TB Disease in HIV-Positive Persons

Prescribe a course of treatment for LTBI for any HIV-infected person with a TST reaction of >5 mm who has no findings of active TB disease and who has not been previously treated. Also, give treatment prophylaxis to any HIV-infected person who has had recent contact with an infectious TB patient, regardless of their age, TST results, or history of previous TB preventive treatment.[1]

There are several combinations of drugs recommended for treatment of both TB disease and LTBI. Healthcare professionals need to be familiar with the latest treatment guidelines and the interaction of some TB medications, most notably rifampin. Because rifampin induces hepatic enzymes, it may accelerate clearance of drugs metabolized by the liver, including methadone[7] and many of the HIV drugs, especially protease inhibitors and nonnucleoside reverse transcriptase inhibitors.[1] Rifampin also decreases the blood levels and activity of the antiretroviral drugs and methadone. Methadone doses need to be increased to achieve optimal blood levels for effective treatment. Depending on the antiretroviral drug used, rifabutin should be used instead of rifampin. However, because some antiretroviral drugs also increase the blood concentrations of rifabutin markedly (resulting in rifabutin toxicity), the dosage of rifabutin should be decreased.[1,8] Consult the Centers for Disease Control and Prevention's website at www.cdc.gov/nchstp/tb/ for the most up-to-date recommendations.[8] When possible, the treatment of TB in HIV-infected persons should be directed by (or should be done in consultation with) a clinician with experience in the care of patients with both diseases.

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CONTINUED FROM LIFESTYLES 80

RECREATIONAL / STREET DRUG / ABUSED PRESCRIPTION	CLINICAL SITUATION	INTERACTION	COMMENTS	REFERENCES
Methadone	HIV infection	Methadone can increase the infectivity of R5 strains of HIV in cell cultures that use the CCR5 co-receptor.	Findings: (1) Methadone up-regulates (increases) CCCR5 expression on cell surfaces. (2) Methadone inhibits the production of beta chemokines that decrease infectivity. (3) Methadone increases cortisol levels, temporarily driving CD4+ cells out of the blood and into lymph nodes and tissues. CD4+ cells return when cortisol levels decrease. (4) Methadone also enhances the activation and replication of latently infected cells.	www.natap.org/2001/may/methadone051601.htm Also see the web site of HarmReduction.org at: www.harmreduction.org/issues/health/haart-meth/haartmethmain.html
Cocaine	HIV infection	Increases viral replication (200x) [9].	May increase the number of CCR5 and CXCR4 receptors on CD4+ cells that HIV uses to infect the cells.	[9] Roth MD, Tashkin DP, et al. Cocaine enhances human immunodeficiency virus replication in a model of severe combined immunodeficient mice implanted with human peripheral blood leukocytes. J Infect Dis 2002; 185(5):701–705.
Ecstasy / X / E / MDMA	HIV infection	One dose of MDMA (100 mg) decreased CD4+ cells by 30% within hours after a single dose. Two doses of MDMA, four hours apart, decreased CD4+ cells by 40% [10].	Additional finding: decreased ability of CD4+ cells to fight infection [10].	[10] Pacifici R, Zuccaro P, et al. Effects of repeated doses of MDMA ("ecstasy") on cell-mediated immune response in humans. Life Sciences 2001; 69:2931–2941.
GHB / Liquid X	HIV infection	Suppresses the immune system		

Editor's Note: Methadone is known to interact with the drugs listed below. Readers are referred to FDA labels for details on these interactions.

METHADONE	PRESCRIPTION MEDICATION	INTERACTION	COMMENTS	REFERENCES
Methadone	AZT / Retrovir® / zidovudine (NRTI)	Increases AZT levels by 50% in blood.	Dose reduction of AZT not recommended routinely.	See FDA label at: www.gsk.com/products/retrovir_us.htm
Methadone	d4T / Zerit® / stavudine (NRTI)	Decreases d4T levels by 13% in blood.	No dose reduction recommended according to FDA label.	See FDA label at: www.zerit.com
Methadone	ddI / Videx® / didanosine (NRTI)	Decreases ddI levels by 52% in blood.	No dosing recommendations for ddI EC according to FDA label.	See FDA label at: www.videxec.com
Methadone	EFV / Sustiva® / efavirenz (NNRTI)	Decreases methadone levels by 60% in blood.	Patients taking methadone and efavirenz may exhibit signs of narcotic withdrawal and methadone dose should be adjusted upward accordingly as noted in FDA label.	See FDA label at: www.sustiva com
Methadone	LPV-r / Kaletra™ / lopinavir + ritonavir	Decreases methadone levels by 53% in blood.	Dosage of methadone may need to be increased when taking lopinavir + ritonavir with methadone according to FDA label.	See FDA label at: www.kaletra.com
Methadone	NFV / Viracept® / nelfinavir	Decreases methadone levels approximately 40% In blood.	No dosing recommendations for nelfinavir according to FDA label.	See FDA label at: www.viracept.com
Methadone	NVP / Viramune® / nevirapine	Decreases methadone levels by 60% in blood.	Patients taking methadone and nevirapine may exhibit signs of narcotic withdrawal, and methadone dose should be adjusted upward accordingly as noted in FDA label.	See FDA label at: www.viramune.com
Methadone	RTV / Norvir® / ritonavir	Decreases methadone levels by 40% in blood.	Dosage increase of methadone may be considered according to FDA label.	See FDA label at: www.norvir.com

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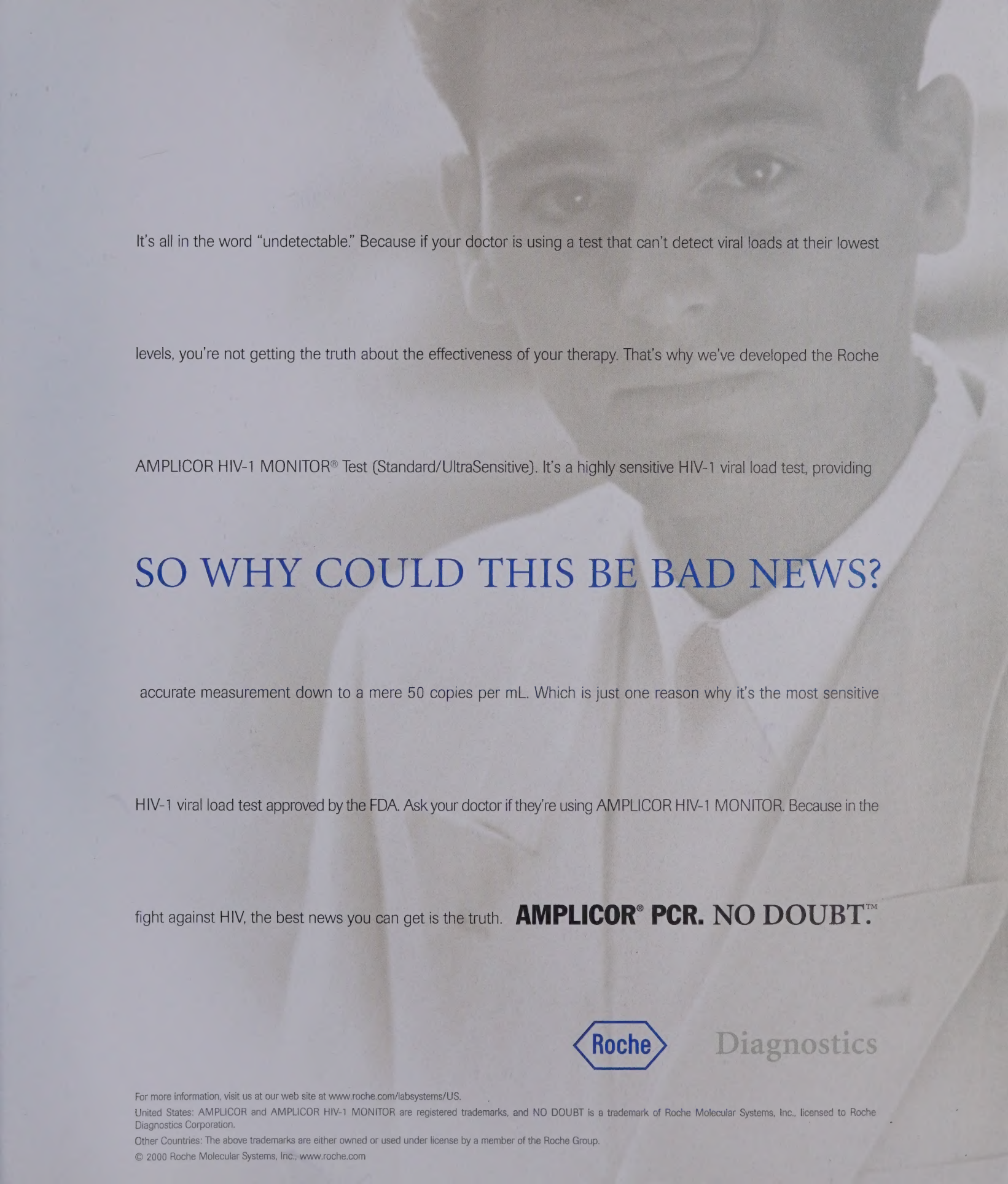

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